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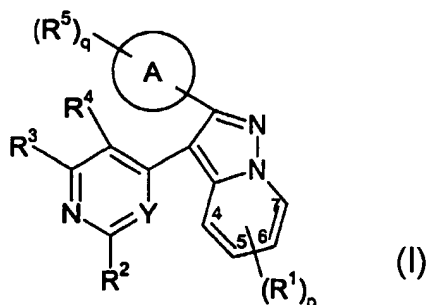
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(54) Title: PYRAZOLO-PYRIDINE DERIVATIVES AS ANTIHERPES AGENTS



(57) Abstract: The present invention provides compounds of formula (I): Insert Formula (I) herewithin all variables are as defined herein, pharmaceutical compositions containing the same, processes for preparing the same and their use as pharmaceutical agents.

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## PYRAZOLO-PYRIDINE DERIVATIVES AS ANTIHERPES AGENTS

## BACKGROUND OF THE INVENTION

- 5 The present invention relates to novel compounds, pharmaceutical formulations comprising these compounds, and the use of these compounds in therapy. More particularly, the present invention relates to compounds for the prophylaxis and treatment of herpes viral infections.
- 10 Of the DNA viruses, those of the herpes group are the sources of the most common viral illnesses in man. The group includes herpes simplex virus types 1 and 2 (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus type 6 (HHV-6), human herpes virus type 7 (HHV-7) and human herpes virus type 8 (HHV-8). HSV-1 and HSV-2 are some of the most common infectious
- 15 agents of man. Most of these viruses are able to persist in the host's neural cells; once infected, individuals are at risk of recurrent clinical manifestations of infection which can be both physically and psychologically distressing.

Herpes simplex viruses (HSV-1 and -2) are the causative agents of herpes labialis and

20 genital herpes. HSV infection is often characterised by extensive and debilitating lesions of the skin, mouth and/or genitals. Primary infections may be subclinical although tend to be more severe than infections in individuals previously exposed to the virus. Ocular infection by HSV can lead to keratitis or cataracts thereby endangering the host's sight. Infection in the new-born, in immunocompromised

25 patients or penetration of the infection into the central nervous system can prove fatal. In the US alone, 40 million individuals are infected with HSV-2, a number that is expected to increase to 60 million by 2007. Over 80% of individuals infected with HSV-2 are unaware they carry and spread the virus, and of those diagnosed less than 20% received oral therapies. The net result is that less than 5% of the infected

30 population are treated. Likewise of the 530 million individuals worldwide who carry the HSV-1 virus, 81% of the symptomatic population remain untreated. No cure

exists for HSV infection, and once infected, individuals carry the virus for life in a dormant state. Reactivation of the virus from latency occurs periodically and may be triggered by stress, environmental factors, and/or suppression of the host immune system. Currently, the use of nucleoside analogs such as valaciclovir (VALTREX®) and aciclovir (ZOVIRAX®) is the standard of care for managing genital herpes virus outbreaks.

VZV is a herpes virus which causes chickenpox and shingles. Chickenpox is the primary disease produced in a host without immunity, and in young children is usually a mild illness characterised by a vesicular rash and fever. Shingles or zoster is the recurrent form of the disease which occurs in adults who were previously infected with VZV. The clinical manifestations of shingles are characterised by neuralgia and a vesicular skin rash that is unilateral and dermatomal in distribution. Spread of inflammation may lead to paralysis or convulsions. Coma can occur if the meninges become affected. VZV is of serious concern in patients receiving immunosuppressive drugs for transplant purposes or for treatment of malignant neoplasia and is a serious complication of AIDS patients due to their impaired immune system.

In common with other herpes viruses, infection with CMV leads to a lifelong association of virus and host. Congenital infection following infection of the mother during pregnancy may give rise to clinical effects such as death or gross disease (microcephaly, hepatosplenomegaly, jaundice, mental retardation), retinitis leading to blindness or, in less severe forms, failure to thrive, and susceptibility to chest and ear infections. CMV infection in patients who are immunocompromised for example as a result of malignancy, treatment with immunosuppressive drugs following transplantation or infection with Human Immunodeficiency Virus, may give rise to retinitis, pneumonitis, gastrointestinal disorders and neurological diseases. CMV infection is also associated with cardiovascular diseases and conditions including restenosis and atherosclerosis.

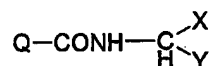
The main disease caused by EBV is acute or chronic infectious mononucleosis (glandular fever). Examples of other EBV or EBV associated diseases include lymphoproliferative disease which frequently occurs in persons with congenital or acquired cellular immune deficiency, X-linked lymphoproliferative disease which  
 5 occurs namely in young boys, EBV-associated B-cell tumours, Hodgkin's disease, nasopharyngeal carcinoma, Burkitt lymphoma, non-Hodgkin's lymphoma, thymomas and oral hairy leukoplakia. EBV infections have also been found in association with a variety of epithelial-cell-derived tumours of the upper and lower respiratory tracts including the lung. EBV infection has also been associated with other diseases and  
 10 conditions including chronic fatigue syndrome and multiple sclerosis.

HHV-6 has been shown to be a causative agent of infantum subitum in children and of kidney rejection and interstitial pneumonia in kidney and bone marrow transplant patients, respectively, and may be associated with other diseases such as multiple  
 15 sclerosis. There is also evidence of repression of stem cell counts in bone marrow transplant patients. HHV-7 is of undetermined disease aetiology.

Hepatitis B virus (HBV) is a viral pathogen of world-wide major importance. The virus is aetiologically associated with primary hepatocellular carcinoma and is thought to  
 20 cause 80% of the world's liver cancer. Clinical effects of infection with HBV range from headache, fever, malaise, nausea, vomiting, anorexia and abdominal pains. Replication of the virus is usually controlled by the immune response, with a course of recovery lasting weeks or months in humans, but infection may be more severe leading to persistent chronic liver disease outlined above.

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U.S. Patent No. 5,498,774 and European Patent No. 0 404 190 to Mitsudera et al., relates to condensed heterocyclic compounds of the general formula (I):



30 wherein Q is a condensed heterocyclic group having a nitrogen atom in the bridgehead which is unsubstituted or substituted, X is a hydrogen atom or a group

attached through C, O, S or N, and Y is an electron attractive group; or its salt which is useful as an agricultural chemical.

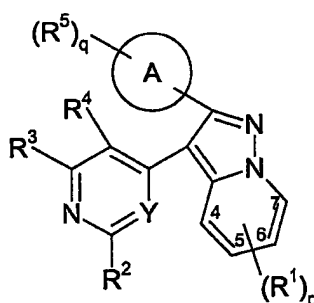
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## BRIEF SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a compound of formula

(I):

10



wherein:

p is 0, 1, 2, 3 or 4;

15

each R<sup>1</sup> is the same or different and is independently selected from the group

consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAr, -OR<sup>10</sup>Ar, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)Ar, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ar, -C(O)NHR<sup>10</sup>Ar, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>,  
 -C(NH)NR<sup>7</sup>R<sup>8</sup>, -C(NH)NR<sup>7</sup>Ar, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ar, -S(O)<sub>n</sub>Het, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>,  
 -S(O)<sub>2</sub>NR<sup>7</sup>Ar, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ar, -NHHet, -NHR<sup>10</sup>Ar, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,  
 -R<sup>10</sup>Ar, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)Ar, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,  
 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ar,  
 -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NHCR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>Ar, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and

25

azido;

or two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group containing 1 or 2 heteroatoms;

each R<sup>7</sup> and R<sup>8</sup> are the same or different and are independently selected from

30

the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  
 -C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>11</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>9</sup>R<sup>11</sup>, -SO<sub>2</sub>R<sup>10</sup>,

-SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;

5 each R<sup>9</sup> and R<sup>11</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, cycloalkyl, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OH,  
 -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> wherein w is 1-10, and -R<sup>10</sup>NR<sup>10</sup>R<sup>10</sup>;

each R<sup>10</sup> is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

10 Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N or CH;

R<sup>2</sup> is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

15 Ay, Het, -OR<sup>7</sup>, -OAy, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het,  
 -S(O)<sub>n</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and  
 -R<sup>10</sup>NR<sup>7</sup>Ay;

n is 0, 1 or 2;

R<sup>3</sup> and R<sup>4</sup> are the same or different and are each independently selected from the

20 group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het, -OR<sup>7</sup>, -OAy,  
 -C(O)R<sup>7</sup>, C(O)Ay, -CO<sub>2</sub>R<sup>7</sup>, -CO<sub>2</sub>Ay, -SO<sub>2</sub>NHR<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet,  
 -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>7</sup>, -R<sup>10</sup>OAy, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ay;

Ring A is a 5-10 membered heterocyclic or heteroaryl group;

q is 0, 1, 2, 3, 4 or 5; and

each R<sup>5</sup> is the same or different and is independently selected from the group

25 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAy, -OR<sup>10</sup>Ay, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)Ay, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>,  
 -C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet,  
 -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>Het, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 30 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay, -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>,  
 -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>,

$-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

wherein when Y is CH,  $R^3$  is not  $-NR^7Ay$ ;

or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

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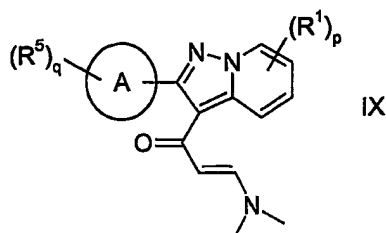
According to a second aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I). The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier or diluent. The pharmaceutical composition may further comprise an antiviral agent. In one  
10 embodiment, the pharmaceutical composition further comprises an antiviral agent selected from the group consisting of aciclovir and valaciclovir.

According to a third aspect, the present invention provides a method for the prophylaxis or treatment of a herpes viral infection in an animal. The method  
15 comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. The herpes viral infection may be selected from the group consisting of herpes simplex virus 1, herpes simplex virus 2, cytomegalovirus, Epstein Barr Virus, herpes zoster virus, human herpes virus 6, human  
20 herpes virus 7 and human herpes virus 8.

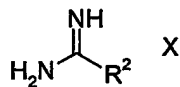
According to a fourth aspect, the present invention provides a method for the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal, comprising administering to the animal a therapeutically  
25 effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

According to a fifth aspect, the present invention provides a process for preparing a compound of formula (I) wherein Y is N and  $R^3$  and  $R^4$  are H. The process comprises  
30 reacting a compound of formula (IX):

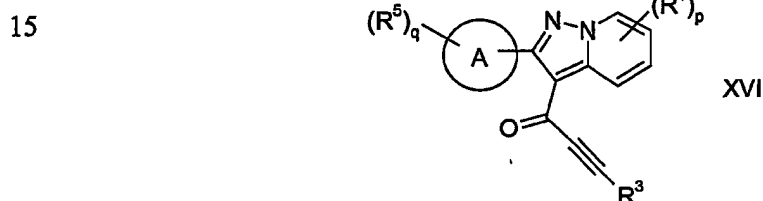
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5 with a compound of formula (X):



According to a sixth aspect, the present invention provides a process for preparing a  
 10 compound of formula (I) wherein Y is N; R<sup>3</sup> is selected from the group consisting of of  
 H, alkyl, cycloalkyl, alkenyl, Ay, Het, -OR<sup>7</sup>, -OAy, -C(O)R<sup>7</sup>, C(O)Ay, -CO<sub>2</sub>R<sup>7</sup>, -CO<sub>2</sub>Ay,  
 -SO<sub>2</sub>NHR<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup> (where R<sup>7</sup> and R<sup>8</sup> are not H), -NR<sup>7</sup>Ay (where R<sup>7</sup> is not H),  
 -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>7</sup>, -R<sup>10</sup>OAy, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ay; and R<sup>4</sup> is H. The process  
 comprises reacting a compound of formula (XVI):

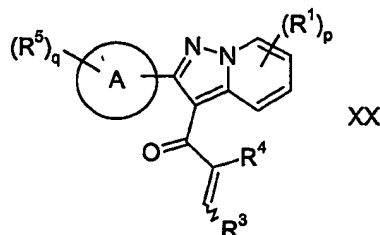


with a compound of formula (X):



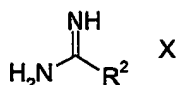
According to a seventh aspect, the present invention provides a process for preparing  
 a compound of formula (I) wherein Y is N. The process comprises reacting a  
 25 compound of formula (XX):

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with a compound of formula (X):

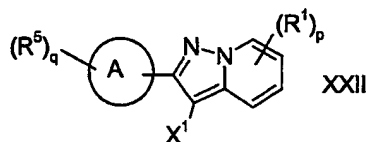


followed by oxidative aromatization.

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According to an eighth aspect, the present invention provides a process for preparing a compound of formula (I). The process comprises reacting a compound of formula (XXII):

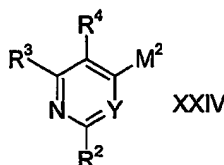
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wherein  $X^1$  is chloro, bromo or iodo;

with a compound of formula (XXIV):

20

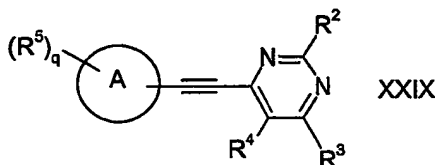


wherein  $M^2$  is  $-B(OH)_2$ ,  $-B(ORa)_2$ ,  $-B(Ra)_2$ ,  $-Sn(Ra)_3$ , Zn-halide, ZnRa, or Mg-

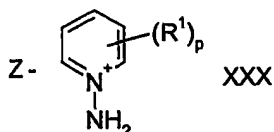
halide where Ra is alkyl or cycloalkyl and halide is halo.

According to a ninth aspect, the present invention provides a process for preparing a compound according of formula (I). The process comprises reacting a compound of formula (XXIX):

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with a 1-aminopyridinium salt of formula (XXX):

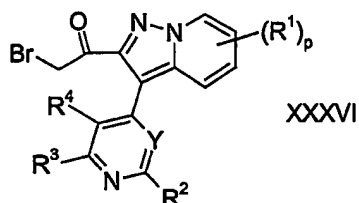


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wherein Z- is a counter ion.

According to a tenth aspect, the present invention provides a process for preparing a compound of formula (I). The process comprises reacting a compound of formula (XXXVI):

10



15 with a suitable ring forming reagent.

In another aspect, the present invention provides a radiolabeled compound of formula (I) or a salt, solvate or physiologically functional derivative thereof. In one embodiment, the present invention provides a tritiated compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

20

In another aspect, the present invention provides a compound of formula (I) for use in therapy.

25

In yet another aspect, the present invention provides a compound of formula (I) for use in the prophylaxis or treatment of a herpes viral infection.

In another aspect, the present invention provides a pharmaceutical composition for use in the prophylaxis or treatment of a herpes viral infection in an animal, such as a human, comprising a compound of formula (I).

30

In yet another aspect, the present invention provides a compound of formula (I) for use in the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal, such as a human.

- 5 In yet another aspect, the present invention provides a pharmaceutical composition for use in the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal, comprising a compound of formula (I).

- 10 In yet another aspect, the present invention provides the use of a compound of formula (I) for the preparation of a medicament for the prophylaxis or treatment of a herpes viral infection in an animal, such as a human.

- 15 In yet another aspect, the present invention provides the use of a compound of formula (I) for the preparation of a medicament for the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal, such as a human.

#### DETAILED DESCRIPTION OF THE INVENTION

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- As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. Similarly, with respect to isolatable intermediates such as compounds of formula (IX), (XVI), (XX), (XXII), (XXIX) and (XXXVI),  
25 the phrase "a compound of formula (*number*)" means a compound having that formula or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

- 30 As used herein, the terms "alkyl" and "alkylene" refer to straight or branched hydrocarbon chains containing from 1 to 8 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl,

isobutyl, isopropyl, and tert-butyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" and "alkylene" also include substituted alkyl and substituted alkylene. The alkyl or alkylene groups may be optionally substituted with one or more substituents selected from the group consisting of mercapto, nitro, cyano, and halo. Perhaloalkyl, such as trifluoromethyl is one particular alkyl group.

As used herein, the term "cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may be optionally substituted on any available carbon with one or more substituents selected from the group consisting of mercapto, nitro, cyano, halo, and alkyl.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing from 2 to 8 carbon atoms and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to ethenyl and propenyl. "Alkenyl" also includes substituted alkenyl. The alkenyl groups may be optionally substituted on any available carbon with one or more substituents selected from the group consisting of mercapto, nitro, cyano, halo, and alkyl.

As used herein, the term "cycloalkenyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example cyclobutenyl, cyclopentenyl and cyclohexenyl. "Cycloalkenyl" also includes substituted cycloalkenyl. The cycloalkenyl may be optionally substituted on any available carbon with one or more substituents selected from the group consisting of mercapto, nitro, cyano, halo, and alkyl.

As used herein, the term "alkynyl" refers to straight or branched hydrocarbon chains containing from 2 to 8 carbon atoms and at least one and up to three carbon-carbon triple bonds. Examples of "alkynyl" as used herein include, but are not limited to ethynyl and propynyl. "Alkynyl" also includes substituted alkynyl. The alkynyl groups  
5 may be optionally substituted on any available carbon with one or more substituents selected from the group consisting of mercapto, nitro, cyano, and halo.

The term "halo" or "halogen" refers to fluorine, chlorine, bromine and iodine.

- 10 The term "aryl" refers to monocyclic carbocyclic groups and fused bicyclic carbocyclic groups having from 5 to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include but are not limited to phenyl, and naphthyl. "Aryl" also includes substituted aryl. Aryl rings may be optionally substituted with substituents selected from the group consisting of halo, alkyl (including perhaloalkyl,  
15 e.g., perfluoroalkyl), alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy, alkylhydroxy, alkylamine, carboxy, carboxamide, sulfonamide, Het, amidine, cyano, nitro and azido. Preferred aryl groups according to the invention include but are not limited to phenyl and substituted phenyl.
- 20 The term "heterocyclic" or "heterocycle" refers to monocyclic saturated or unsaturated non-aromatic groups and fused bicyclic non-aromatic groups, having the specified number of members (e.g. carbon and heteroatoms N and/or O and/or S) and containing 1, 2, 3 or 4 heteroatoms selected from N, O and S. Examples of particular heterocyclic groups include but are not limited to tetrahydrofuran, dihydropyran,  
25 tetrahydropyran, pyran, oxetane, thietane, 1,4-dioxane, 1,3-dioxane, 1,3-dioxalane, piperidine, piperazine, tetrahydropyrimidine, pyrrolidine, morpholine, thiomorpholine, thiazolidine, oxazolidine, tetrahydrothiopyran, tetrahydrothiophene, and the like. "Heterocyclic" also includes substituted heterocyclic. The heterocyclic group may be optionally substituted with substituents selected from the group consisting of halo,  
30 alkyl (including perhaloalkyl, e.g., perfluoroalkyl), alkenyl, cycloalkyl, cycloalkenyl, perfluoroalkyl, alkoxy, amino, hydroxy, alkylhydroxy, alkylamine, carboxy, carboxamide,

sulfonamide, Het, amidine, cyano, nitro and azido. Preferred heterocyclic groups according to the invention include but are not limited to substituted and unsubstituted tetrahydrofuran, pyrrolidine, piperidine, morpholine, thiomorpholine and piperazine, and substituted variants thereof.

5

The term "heteroaryl" refers to aromatic monocyclic groups and aromatic fused bicyclic groups having the specified number of members (e.g. carbon and heteroatoms N and/or O and/or S) and containing 1, 2, 3, or 4 heteroatoms selected from N, O and S. Examples of particular heteroaryl groups include but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole.

10

"Heteroaryl" also includes substituted heteroaryl. The heteroaryl group may be optionally substituted with substituents selected from the group consisting of halo, alkyl (including perhaloalkyl, e.g., perfluoroalkyl), alkenyl, cycloalkyl, cycloalkenyl, perfluoroalkyl, alkoxy, amino, hydroxy, alkylhydroxy, alkylamine, carboxy, carboxamide, sulfonamide, Het, amidine, cyano, nitro and azido. Preferred heteroaryl groups according to the invention include but are not limited to substituted and unsubstituted pyridine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole and pyrimidine, and substituted variants thereof.

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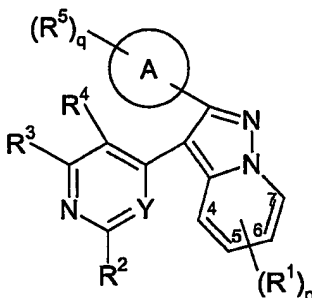
The term "members" (and variants thereof e.g., "membered") in the context of heterocyclic and heteroaryl groups refers to the total atoms, carbon and heteroatoms N, O and/or S, which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine and an example of a 6-membered heteroaryl ring is pyridine.

25

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and events that do not occur.

30

The present invention provides compounds of formula (I):



wherein:

p is 0, 1, 2, 3 or 4;

- 10 each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAr$ ,  $-OR^{10}Ar$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)Ar$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  $-C(NH)NR^7Ar$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAr$ ,  $-S(O)_nHet$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ar$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}Ar$ ,  $-R^{10}Het$ ,  $-R^{10}O-C(O)R^9$ ,  $-R^{10}O-C(O)Ar$ ,  $-R^{10}O-C(O)Het$ ,  $-R^{10}O-S(O)_nR^9$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ar$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ar$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;
- 20 or two adjacent  $R^1$  groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group containing 1 or 2 heteroatoms;
- each  $R^7$  and  $R^8$  are the same or different and are independently selected from
- 25 the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  $-C(O)R^9$ ,  $-CO_2R^9$ ,  $-C(O)NR^9R^{11}$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^9R^{11}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^9R^{11}$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^{10}$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^9R^{11}$ ,  $-R^{10}NHCOR^9$ ,  $-R^{10}NHSo_2R^9$  and  $-R^{10}NHC(NH)NR^9R^{11}$ ;
- 30 each  $R^9$  and  $R^{11}$  are the same or different and are independently selected from

the group consisting of H, alkyl, cycloalkyl,  $-R^{10}$ cycloalkyl,  $-R^{10}OH$ ,  
 $-R^{10}(OR^{10})_w$  wherein w is 1-10, and  $-R^{10}NR^{10}R^{10}$ ;

each  $R^{10}$  is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

5 Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N or CH;

$R^2$  is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

10 Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAy$ ,  $-S(O)_nHet$ ,  
 $-S(O)_nNR^7R^8$ ,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}NR^7R^8$  and  
 $-R^{10}NR^7Ay$ ;

n is 0, 1 or 2;

$R^3$  and  $R^4$  are the same or different and are each independently selected from the

15 group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  
 $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  
 $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

Ring A is a 5-10 membered heterocyclic or heteroaryl group;

q is 0, 1, 2, 3, 4 or 5; and

each  $R^5$  is the same or different and is independently selected from the group

20 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  
 $-OAY$ ,  $-OR^{10}Ay$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)AY$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  
 $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ay$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  
 $-C(NH)NR^7Ay$ ,  $-S(O)_nR^9$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ay$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  
 $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}Het$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  
 25  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ay$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  
 $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  
 $-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

wherein when Y is CH,  $R^3$  is not  $-NR^7Ay$ ;

or a pharmaceutically acceptable salt, solvate or physiologically functional derivative

30 thereof.

In one embodiment, the compounds of formula (I) are defined wherein p is 0, 1 or 2. More particularly, p is 1 or 2. In one embodiment of the present invention, the compounds of formula (I) are defined wherein p is 1. In one embodiment of the present invention, the compounds of formula (I) are defined wherein p is 2.

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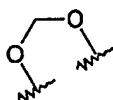
R<sup>1</sup> may be located at any of the C-4, C-5, C-6 and/or C-7 positions on the pyrazolopyridine ring.

In one embodiment of the invention wherein p is 1 or more, at least one R<sup>1</sup> contains  
 10 an aryl, heterocyclic or heteroaryl moiety (e.g., at least one R<sup>1</sup> is selected from the group consisting of Ay, Het, -O<sub>Ay</sub>, -OR<sup>10</sup><sub>Ay</sub>, -OHet, -OR<sup>10</sup><sub>Het</sub>, -C(O)<sub>Ay</sub>, -C(O)<sub>Het</sub>, -C(O)NR<sup>7</sup><sub>Ay</sub>, -C(O)NHR<sup>10</sup><sub>Ay</sub>, -C(O)NHR<sup>10</sup><sub>Het</sub>, -C(NH)NR<sup>7</sup><sub>Ay</sub>, -S(O)<sub>n</sub><sub>Ay</sub>, -S(O)<sub>n</sub><sub>Het</sub>, -S(O)<sub>2</sub>NR<sup>7</sup><sub>Ay</sub>, -NR<sup>7</sup><sub>Ay</sub>, -NHHet, -NHR<sup>10</sup><sub>Ay</sub>, -NHR<sup>10</sup><sub>Het</sub>, -R<sup>10</sup><sub>Ay</sub>, -R<sup>10</sup><sub>Het</sub>, -R<sup>10</sup>O-C(O)<sub>Ay</sub>, -R<sup>10</sup>O-C(O)<sub>Het</sub>, -R<sup>10</sup>C(O)NR<sup>7</sup><sub>Ay</sub>, -R<sup>10</sup>C(O)NHR<sup>10</sup><sub>Het</sub> and -R<sup>10</sup>NR<sup>7</sup><sub>Ay</sub>, or any subset  
 15 thereof). In another embodiment, compounds of formula (I) are defined wherein at least one R<sup>1</sup> contains a heterocyclic or heteroaryl moiety (e.g., at least one R<sup>1</sup> is selected from the group consisting of Het, -OHet, -OR<sup>10</sup><sub>Het</sub>, -C(O)<sub>Het</sub>, -C(O)NHR<sup>10</sup><sub>Het</sub>, -S(O)<sub>n</sub><sub>Het</sub>, -NHHet, -NHR<sup>10</sup><sub>Het</sub>, -R<sup>10</sup><sub>Het</sub>, -R<sup>10</sup>O-C(O)<sub>Het</sub> and -R<sup>10</sup>C(O)NHR<sup>10</sup><sub>Het</sub>, or any subset thereof). In yet another embodiment, the compounds  
 20 of formula (I) are defined wherein no R<sup>1</sup> contains an aryl, heterocyclic or heteroaryl moiety (e.g., each R<sup>1</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -OR<sup>7</sup>, -C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 25 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and azido; or any subset thereof). In another embodiment, no R<sup>1</sup> contains a heteroaryl or heterocyclic moiety but may contain an aryl moiety (e.g., each R<sup>1</sup> is the same or different and is independently selected from the group consisting of halo, alkyl,  
 30 alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, -OR<sup>7</sup>, -O<sub>Ay</sub>, -OR<sup>10</sup><sub>Ay</sub>, -C(O)R<sup>9</sup>, -C(O)<sub>Ay</sub>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup><sub>Ay</sub>, -C(O)NHR<sup>10</sup><sub>Ay</sub>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>,

-C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHR<sup>10</sup>Ay, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>Ay, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)Ay, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCO<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>Ay, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and azido, or any subset thereof).

One class of compounds of formula (I) includes those compounds defined wherein two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group containing 1 or 2 heteroatoms.

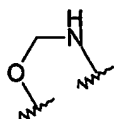
- By "two adjacent R<sup>1</sup> groups" is meant that two R<sup>1</sup> groups are bonded to adjacent carbon atoms. When two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group having 1 or 2 heteroatoms, each R<sup>1</sup> group may be the same or different and is selected from the group consisting of alkyl, -OR<sup>7</sup>, -NR<sup>7</sup>R<sup>8</sup>, and -S(O)<sub>n</sub>R<sup>9</sup>. For example, in one embodiment two adjacent R<sup>1</sup> groups are -OR<sup>7</sup> and together with the carbon atoms to which they are bonded, they form a heterocyclic group such as:



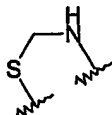
- In another embodiment, two adjacent R<sup>1</sup> groups are alkyl and together with the carbon atoms to which they are bonded, they form a cycloalkyl group such as:



- In another embodiment two adjacent R<sup>1</sup> groups are defined as -OR<sup>7</sup> and -NR<sup>7</sup>R<sup>8</sup> respectively and together with the carbon atoms to which they are bonded, they form a heterocyclic group such as:



In another embodiment two adjacent  $R^1$  groups are defined as  $-S(O)_nR^9$  and  $-NR^7R^8$  respectively and together with the carbon atoms to which they are bonded, they form a heterocyclic group such as:



5

From these examples, additional embodiments can be readily ascertained by those skilled in the art.

- 10 In one particular embodiment, two adjacent  $R^1$  groups together with the carbon atoms to which they are bonded do not form a cycloalkyl or a 5- or 6-membered heterocyclic group containing 1 or 2 heteroatoms.

- 15 In one embodiment, each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl, Ay, Het,  $-OR^7$ ,  $-OAr$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-S(O)_nR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}OR^9$ , cyano, nitro and azido, or any subset thereof. More particularly, each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl, Ay, Het,  $-OR^7$ ,  $-C(O)Het$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NHR^{10}Het$ ,  
 20  $-S(O)_nR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}OR^9$  and cyano, or any subset thereof. In one particular embodiment wherein p is 1 or more, each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl, Het,  $-OR^7$ ,  $-C(O)NR^7R^8$ ,  $-S(O)_nR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ar$  and  $-NHHet$ , or any subset thereof. In one embodiment,  $R^1$  is  $-NR^7R^8$ .

25

More specifically, particular compounds of formula (I) are defined wherein p is 1 or more and each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl,  $-NH_2$ ,  $-NH$ -alkyl,  $-NH$ -cycloalkyl,  $-N(alkyl)(alkyl)$ , phenyl, Het,  $-O$ -alkyl,  $-N(alkyl)-O$ -alkyl,  $-NHAy$ ,  $-C(O)NH_2$ ,  $-C(O)NH(alkyl)$ ,

-C(O)N(alkyl)(alkyl) and -S-alkyl, or any subset thereof. More particularly, R<sup>1</sup> is selected from the group consisting of -NH-alkyl, -NH-cycloalkyl and pyrrolidone, or any subset thereof.

- 5 Specific examples of some particular R<sup>1</sup> groups are selected from the group consisting of Cl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, trifluoromethyl, -NH<sub>2</sub>, -NH-methyl, -N(CH<sub>3</sub>)<sub>2</sub>, -NH-cyclopentyl, -NH-cyclopropyl, -NH-isopropyl, -NH-butyl, -NH-phenyl, -N(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, pyrrolidine, methoxy, ethoxy, propoxy, isopropoxy, butoxy, thiomethoxy, thioethoxy, thioisopropoxy, and pyrrolidine, or any subset thereof.

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- In one embodiment, R<sup>7</sup> and R<sup>8</sup> are each the same or different and are each independently selected from the group consisting of H, alkyl, cycloalkyl, -C(O)R<sup>9</sup>, -R<sup>10</sup>-cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup> and -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, or any subset thereof. More particularly, R<sup>7</sup> and R<sup>8</sup> are each the same or different and are each independently  
15 selected from the group consisting of H, alkyl, cycloalkyl, and -R<sup>10</sup>-cycloalkyl, or any subset thereof. In one embodiment, R<sup>7</sup> and R<sup>8</sup> are each the same or different and are each independently selected from the group consisting of H, alkyl and cycloalkyl.

- The group -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> in the definition of R<sup>9</sup> and R<sup>11</sup> refers to a PEG-like chain. In one  
20 embodiment, R<sup>9</sup> and R<sup>11</sup> are each the same or different and are each independently selected from the group consisting of H, alkyl, cycloalkyl, and -R<sup>10</sup>-cycloalkyl, or any subset thereof. More particularly, R<sup>9</sup> and R<sup>11</sup> are each the same or different and are each independently selected from the group consisting of H and alkyl.

- 25 In one embodiment, R<sup>10</sup> is alkyl or cycloalkyl. In one embodiment, R<sup>10</sup> is alkyl. In another embodiment, the compounds of formula (I) include those compounds defined where R<sup>2</sup> does not contain an aryl, heterocyclic or heteroaryl moiety (or in one embodiment, R<sup>2</sup> does not contain a heterocyclic or heteroaryl moiety but may contain an aryl moiety). A particular embodiment includes those compounds of formula (I)  
30 where R<sup>2</sup> does contain an aryl, heterocyclic or heteroaryl moiety. Based on the guidance given above for R<sup>1</sup>, one skilled in the art can readily determine the list of

appropriate groups defining  $R^2$  which contain or exclude aryl, heterocyclic or heteroaryl moieties.

In one embodiment,  $R^2$  is selected from the group consisting of Aryl, Het,  
5 -OR<sup>7</sup>, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Het and -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, or any subset thereof. In one particular embodiment,  $R^2$  is selected from the group consisting of Het, -NR<sup>7</sup>R<sup>8</sup>, -NHHet and -NHR<sup>10</sup>Het, or any subset thereof. In one particular embodiment, the compounds of formula (I) are defined wherein  $R^2$  is selected from the group consisting of -NR<sup>7</sup>R<sup>8</sup> and Het.

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More specifically, in one embodiment,  $R^2$  is selected from the group consisting of -NH<sub>2</sub>, -NH-alkyl, -NH-cycloalkyl, -N(alkyl)(alkyl), Het, -O-alkyl, -N(alkyl)-O-alkyl, and -S-alkyl, or any subset thereof.

15 Specific examples of particular  $R^2$  groups are selected from the group consisting of -NH<sub>2</sub>, cyclopentylamine, cyclopropylamine, n-butylamine, pyrrolidine, -NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -S-methyl, S-ethyl, and O-butyl, or any subset thereof.

In one class of compounds of formula (I), Y is CH. In another preferred class of  
20 compounds of formula (I), Y is N.

In another embodiment, the compounds of formula (I) include those compounds defined where at least one of  $R^3$  and  $R^4$  contains an aryl, heterocyclic or heteroaryl moiety (or contains a heterocyclic or heteroaryl moiety but exclude aryl moieties).  
25 Another embodiment includes those compounds of formula (I) where neither  $R^3$  nor  $R^4$  contain an aryl, heterocyclic or heteroaryl moiety (or neither contains a heterocyclic or heteroaryl moiety but may contain an aryl moiety). Based on the guidance given above for  $R^1$ , one skilled in the art can readily determine the list of appropriate groups defining  $R^3$  and  $R^4$  which contain or exclude aryl, heterocyclic and/or heteroaryl  
30 moieties.

In one embodiment,  $R^3$  is selected from the group consisting of H, halo, alkyl,  $Ay$ ,  $-OR^7$ ,  $-CO_2R^7$ ,  $-NR^7R^8$ ,  $-R^{10}OR^7$  and  $-R^{10}NR^7R^8$ , or any subset thereof. More particularly,  $R^3$  is selected from the group consisting of H, halo, alkyl,  $-OR^7$ , and  $-NR^7R^8$ , or any subset thereof. In one particular embodiment,  $R^3$  is H or alkyl. In one embodiment  $R^3$  is H. In  
5 one particular embodiment, when Y is CH,  $R^3$  is not  $-NR^7Ay$ .

In one embodiment,  $R^4$  is selected from the group consisting of H, halo, alkyl,  $Ay$ ,  $-OR^7$ ,  $-CO_2R^7$ ,  $-NR^7R^8$ ,  $-R^{10}OR^7$  and  $-R^{10}NR^7R^8$ , or any subset thereof. More particularly,  $R^4$  is selected from the group consisting of H, halo, alkyl,  $-OR^7$ , and  $-NR^7R^8$ , or any subset  
10 thereof. In one embodiment,  $R^4$  is H or alkyl. In one embodiment  $R^4$  is H.



in formula (I) above is herein referred to as Ring A.

Ring A is a heterocyclic or heteroaryl group having from 5 to 10 members (including  
15 1, 2, 3 or 4 heteroatoms selected from N, O and S).

Ring A may be bonded to the pyrazolopyridine core through any available atom including any available heteroatom. In one embodiment, Ring A contains at least one N atom and is bonded to the pyrazolopyridine core through N.

20

Examples of heterocyclic or heteroaryl groups having 5-10 members which are suitable as Ring A are selected from the group consisting of furan, pyridine, pyrimidine, thiazole, pyrazine, pyrrole, imidazole, oxazole, benzimidazole, quinoline, isoquinoline, and quinoxoline, or any subset thereof.

25

In one embodiment, Ring A is a heterocyclic or heteroaryl group having 9 members. In one particular embodiment, Ring A is a heterocyclic or heteroaryl group having 5 or 6 members.

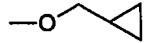
30 In one embodiment, Ring A in formula (I) is selected from the group consisting of furan, thiazole, pyridine and pyrimidine.

In one particular embodiment, q is selected from the group consisting of 0, 1 and 2.

In one embodiment, q is 0. In one embodiment, q is 1.

5  $R^5$  may be in any suitable position on the heterocyclic or heteroaryl ring.  $R^5$  may be bound to a carbon atom or to a suitable heteroatom (i.e., N). One skilled in the art will readily be able to ascertain suitable positions for attachment of the substituent(s)  $R^5$ .

One class of compounds of formula (I) includes those compounds defined wherein at least one of  $R^5$  contains an aryl, heterocyclic or heteroaryl moiety (in one embodiment, a heterocyclic or heteroaryl moiety). Another class of compounds of formula (I) includes those compounds defined wherein no  $R^5$  contains an aryl, heterocyclic or heteroaryl moiety (in one embodiment, a heterocyclic or heteroaryl moiety). Based on the guidance given above for  $R^1$ , one skilled in the art can readily determine the list of appropriate groups defining  $R^5$  which contain or exclude aryl, heterocyclic or heteroaryl moieties.

In one embodiment, each  $R^5$  is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, Aryl, Het,  $-OR^7$ ,  $-OAry$ ,  $-CO_2R^8$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ary$ ,  $-S(O)_2NR^7R^8$ ,  $-NR^7R^8$ ,  $-NR^7Ary$ ,  $-NHR^{10}Ary$ , cyano, nitro and azido, or any subset thereof. More particularly, each  $R^5$  is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, Aryl, Het,  $-OR^7$ ,  $-NR^7R^8$ ,  $-NR^7Ary$ , cyano, nitro, and azido, or any subset thereof. In one particular embodiment, each  $R^5$  is the same or different and is independently selected from the group consisting of halo, alkyl,  $-OR^7$ ,  $-NR^7R^8$ , cyano, nitro, and azido, or any subset thereof. A few specific embodiments of the compounds of formula (I) are defined where  $R^5$  is selected from the group consisting of halo (e.g., fluoro or chloro), alkyl (e.g., methyl), O-alkyl (e.g., O-methyl, O-isobutyl, and ) , O-allyl, cyano,  $-NH-CH_3$ ,  $-N(CH_3)_2$ , nitro and azido, or any subset thereof.

30 It is to be understood that the present invention includes all combinations and subsets of the specifically mentioned and particular groups defined hereinabove.

Specific examples of compounds of formula (I) include but are not limited to:

*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-  
a]pyridin-7-amine;

*N*-Cyclopentyl-3-[2-(methylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-  
a]pyridin-7-amine;

*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-pyridinyl)pyrazolo[1,5-  
a]pyridin-7-amine;

*N*-Cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-a]pyridin-  
3-yl}-2-pyrimidinyl)amine;

*N*-(4-{7-Chloro-2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-a]pyridin-3-yl}-  
2-pyrimidinyl)-*N*-cyclopentylamine;

*N*-Cyclopentyl-2,3-bis[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-a]pyridin-7-  
amine;

*N*-(2-Methoxyethyl)-2,3-bis{2-[(2-methoxyethyl)amino]pyrimidin-4-yl}pyrazolo[1,5-  
a]pyridin-7-amine;

*N*-Butyl-2,3-bis[2-(butylamino)pyrimidin-4-yl]pyrazolo[1,5-a]pyridin-7-amine;

*N*-Cyclopropyl-2,3-bis[2-(cyclopropylamino)pyrimidin-4-yl]pyrazolo[1,5-a]pyridin-7-  
amine;

7-Morpholin-4-yl-2,3-bis(2-morpholin-4-ylpyrimidin-4-yl)pyrazolo[1,5-a]pyridine;

*N*-Isobutyl-2,3-bis[2-(isobutylamino)pyrimidin-4-yl]pyrazolo[1,5-a]pyridin-7-amine;

*N*-Benzyl-2,3-bis[2-(benzylamino)pyrimidin-4-yl]pyrazolo[1,5-a]pyridin-7-amine;

*N*-Isopropyl-2,3-bis[2-(isopropylamino)pyrimidin-4-yl]pyrazolo[1,5-a]pyridin-7-amine;

2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-a]pyridine;

4-[2-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]-*N*-isopropyl-2-

pyrimidinamine;

*N*-Isopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-a]pyridin-3-yl}-2-  
pyrimidinamine;

3-[2-(Cyclopropylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-  
pyridinyl]pyrazolo[1,5-a]pyridin-7-amine;

*N*-Cyclopentyl-2-[2-(cyclopentylamino)-4-pyridinyl]-3-[2-(isopropylamino)-4-  
pyrimidinyl]pyrazolo[1,5-a]pyridin-7-amine;

- 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine;  
 5 *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
 10 *N*-Cyclopropyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
 15 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-cyclopropyl-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
 2-(5-Bromo-2-furyl)-*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine; and  
*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-7-amine;  
 20 and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof.

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. The pharmaceutically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include  
 25 hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic,  
 30

hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic (mesylate), naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steroic, tannic and the like. In one embodiment, the compounds of formula (I) are in the form of the mesylate salt. Other acids such as  
5 oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine,  
10 ethylenediamine, N-methylglucamine and procaine salts.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, or acetic acid.

15

The term "physiologically functional derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide of a compound of formula (I), which upon administration to an animal, particularly a mammal, such as a human, is capable of  
20 providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. See for example, Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice.

Processes for preparing pharmaceutically acceptable salts, solvates and physiologically  
25 functional derivatives of the compounds of formula (I) are conventional in the art. See, e.g., Burger's Medicinal Chemistry And Drug Discovery 5th Edition, Vol 1: Principles And Practice.

As will be apparent to those skilled in the art, in the processes described below for the  
30 preparation of compounds of formula (I), certain intermediates, may be in the form of pharmaceutically acceptable salts, solvates or physiologically functional derivatives of

the compound. Those terms as applied to any intermediate employed in the process of preparing compounds of formula (I) have the same meanings as noted above with respect to compounds of formula (I). Processes for preparing pharmaceutically acceptable salts, solvates and physiologically functional derivatives of such intermediates are known in the art and are analogous to the process for preparing pharmaceutically acceptable salts, solvates and physiologically functional derivatives of the compounds of formula (I).

Certain compounds of formula (I) and intermediates used in the processes of preparing compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centers are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The present invention further provides compounds of formula (I) for use in medical therapy, e.g. in the treatment or prophylaxis, including suppression of recurrence of symptoms, of a viral disease in an animal, e.g. a mammal such as a human. The compounds of formula (I) are especially useful for the treatment or prophylaxis of viral diseases such as herpes viral infections. Herpes viral infections include, for example, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), cytomegalovirus (CMV) (including CMV in organ transplant patients being treated with immunosuppressants), Epstein Barr virus (EBV), varicella zoster virus (VZV), human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7), and human herpes virus 8 (HHV-8). Thus, the compounds of the invention are also useful in the treatment or prophylaxis of the symptoms or effects of herpes virus infections.

The compounds of the invention are useful in the treatment or prophylaxis of conditions or diseases associated with herpes virus infections, particularly conditions or diseases associated with latent herpes virus infections in an animal, e.g., a mammal such as a human. By conditions or diseases associated with herpes viral infections is meant a condition or disease, excluding the viral infection per se, which results from the presence of the viral infection, such as chronic fatigue syndrome which is associated with EBV infection; and multiple sclerosis which has been associated with herpes viral infections such as EBV and HHV-6. Further examples of such conditions or diseases are described in the background section above.

10

In addition to those conditions and diseases, the compounds of the present invention may also be used for the treatment or prophylaxis of cardiovascular diseases and conditions associated with herpes virus infections, in particular atherosclerosis, coronary artery disease and restenosis and specifically restenosis following angioplasty (RFA). Restenosis is the narrowing of the blood vessels which can occur after injury to the vessel wall, for example injury caused by balloon angioplasty or other surgical and/or diagnostic techniques, and is characterized by excessive proliferation of smooth muscle cells in the walls of the blood vessel treated. It is thought that in many patients suffering from restenosis following angioplasty, viral infection, particularly by CMV and/or HHV-6 plays a pivotal role in the proliferation of the smooth muscle cells in the coronary vessel. Restenosis can occur following a number of surgical and/or diagnostic techniques, for example, transplant surgery, vein grafting, coronary by-pass grafting and, most commonly following angioplasty.

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There is evidence from work done both *in vitro* and *in vivo*, indicating that restenosis is a multifactorial process. Several cytokines and growth factors, acting in concert, stimulate the migration and proliferation of vascular smooth muscle cells (SMC) and production of extracellular matrix material, which accumulate to occlude the blood vessel. In addition growth suppressors act to inhibit the proliferation of SMC's and production of extracellular matrix material.

25

30

In addition, compounds of formula (I) may be useful in the treatment or prophylaxis of hepatitis B and hepatitis C viruses, human papilloma virus (HPV) and HIV.

5 The present invention provides a method for the treatment or prophylaxis of a viral infection in an animal such as a mammal (e.g., a human), particularly a herpes viral infection, which method comprises administering to the animal a therapeutically effective amount of the compound of formula (I).

10 As used herein, the term "prophylaxis" refers to the prevention of infection, the prevention of occurrence of symptoms in an infected subject, the prevention of recurrence of symptoms in an infected subject, or a decrease in severity or frequency of symptoms of viral infection, condition or disease in the subject.

15 As used herein, the term "treatment" refers to the partial or total elimination of symptoms or decrease in severity of symptoms of viral infection, condition or disease in the subject, or the elimination or decrease of viral presence in the subject.

20 As used herein, the term "therapeutically effective amount" means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to treat or prevent the stated disease, condition or infection. For example, a therapeutically effective amount of a compound of formula (I) for the treatment of a herpes virus infection is an amount sufficient to treat the herpes virus infection in the subject.

25 The present invention also provides a method for the treatment or prophylaxis of conditions or diseases associated with herpes viral infections in an animal such as a mammal (e.g., a human), which comprises administering to the animal a therapeutically effective amount of the compound of formula (I). In one embodiment, the present invention provides a method for the treatment or prophylaxis of chronic  
30 fatigue syndrome or multiple sclerosis in an animal such as a mammal (e.g., a human), which comprises administering to the animal a therapeutically effective amount of a

compound of formula (I). The foregoing method is particularly useful for the treatment or prophylaxis of chronic fatigue syndrome or multiple sclerosis associated with latent infection with a herpes virus.

- 5 In another embodiment, the present invention provides a method for the treatment or prophylaxis of a cardiovascular condition such as atherosclerosis, coronary artery disease or restenosis (particularly restenosis following surgery such as angioplasty), which comprises administering to the animal a therapeutically effective antiviral amount of the compound of formula (I).

10

The present invention further provides a method for the treatment or prophylaxis of hepatitis B or hepatitis C viruses in an animal such as a mammal (e.g., a human), which comprises administering to the animal a therapeutically effective amount of the compound of formula (I).

15

The present invention further provides a method for the treatment or prophylaxis of human papilloma virus in an animal such as a mammal (e.g., a human), which comprises administering to the animal a therapeutically effective amount of the compound of formula (I).

20

The present invention further provides a method for the treatment or prophylaxis of HIV in an animal such as a mammal (e.g., a human), which comprises administering to the animal a therapeutically effective amount of the compound of formula (I).

- 25 The present invention also provides the use of the compound of formula (I) in the preparation of a medicament for the treatment or prophylaxis of a viral infection in an animal such as a mammal (e.g., a human), particularly a herpes viral infection; the use of the compound of formula (I) in the preparation of a medicament for the treatment of a condition or disease associated with a herpes viral infection; and the  
30 use of the compound of formula (I) in the preparation of a medicament for the treatment or prophylaxis of hepatitis B or hepatitis C viruses, human papilloma virus

or HIV. In particular, the present invention also provides the use of a compound of formula (I) in the preparation of a medicament for the treatment or prophylaxis of chronic fatigue syndrome or multiple sclerosis. In one embodiment, the present invention provides the use of a compound of formula (I) in the preparation of a medicament for the treatment or prophylaxis of cardiovascular disease, such as restenosis or atherosclerosis.

The compounds of formula (I) are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or diluents.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical composition. The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers or diluents together with the compound of formula (I). The carrier(s) or diluents must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides for a pharmaceutical composition or formulation comprising a compound of formula (I). In one embodiment, the pharmaceutical formulation further comprises one or more pharmaceutically acceptable carriers or diluents and, optionally, other therapeutic and/or prophylactic ingredients.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition, age, and disorder of the recipient as well as the viral infection or disease

being treated. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compound(s) ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In  
5 general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation. Formulations suitable for oral administration may be presented as discrete units such as capsules (including soft-gel capsules), cachets or tablets (e.g. chewable tablets in  
10 particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

15 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with other conventional excipients such as binding agents,  
20 (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl  
25 sulfate. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The tablets may be coated according to methods well-known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. Liquid preparations may also be formulated as soft-gel capsules for oral administration, e.g., containing conventional soft-gel excipients such as polyethylene glycol.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical (e.g., dermal) or intranasal administration include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations including petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof.

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Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured base such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a base such as gelatin and glycerin or sucrose and acacia.

10

The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

15

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

20

It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02–5000 mg per day, preferably 100–1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day. The formulations according to the invention

25

30

may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

The compound of formula (I) for use in the instant invention may be used in  
5 combination with other therapeutic agents for example, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors and/or other antiviral agents. The invention thus provides in a further aspect the use of a combination comprising a compound of formula (I) with a further therapeutic agent in the treatment of viral infections. Particular antiviral agents which may be  
10 combined with the compounds of the present invention include aciclovir, valaciclovir, famcyclovir, ganciclovir, docosanol, miribavir, amprenavir, lamivudine, zidovudine, and abacavir. Preferred antiviral agents for combining with the compounds of the present invention include aciclovir, famcyclovir and valaciclovir. Thus the present invention provides in a further aspect, a combination comprising a compound of formula (I) and  
15 an antiviral agent selected from the group consisting of aciclovir or valaciclovir; the use of such combination in the treatment of viral infections and the preparation of a medicament for the treatment of viral infections, and a method of treating viral infections comprising administering a compound of formula (I) and an antiviral agent selected from the group consisting of aciclovir and valaciclovir.  
20

When the compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

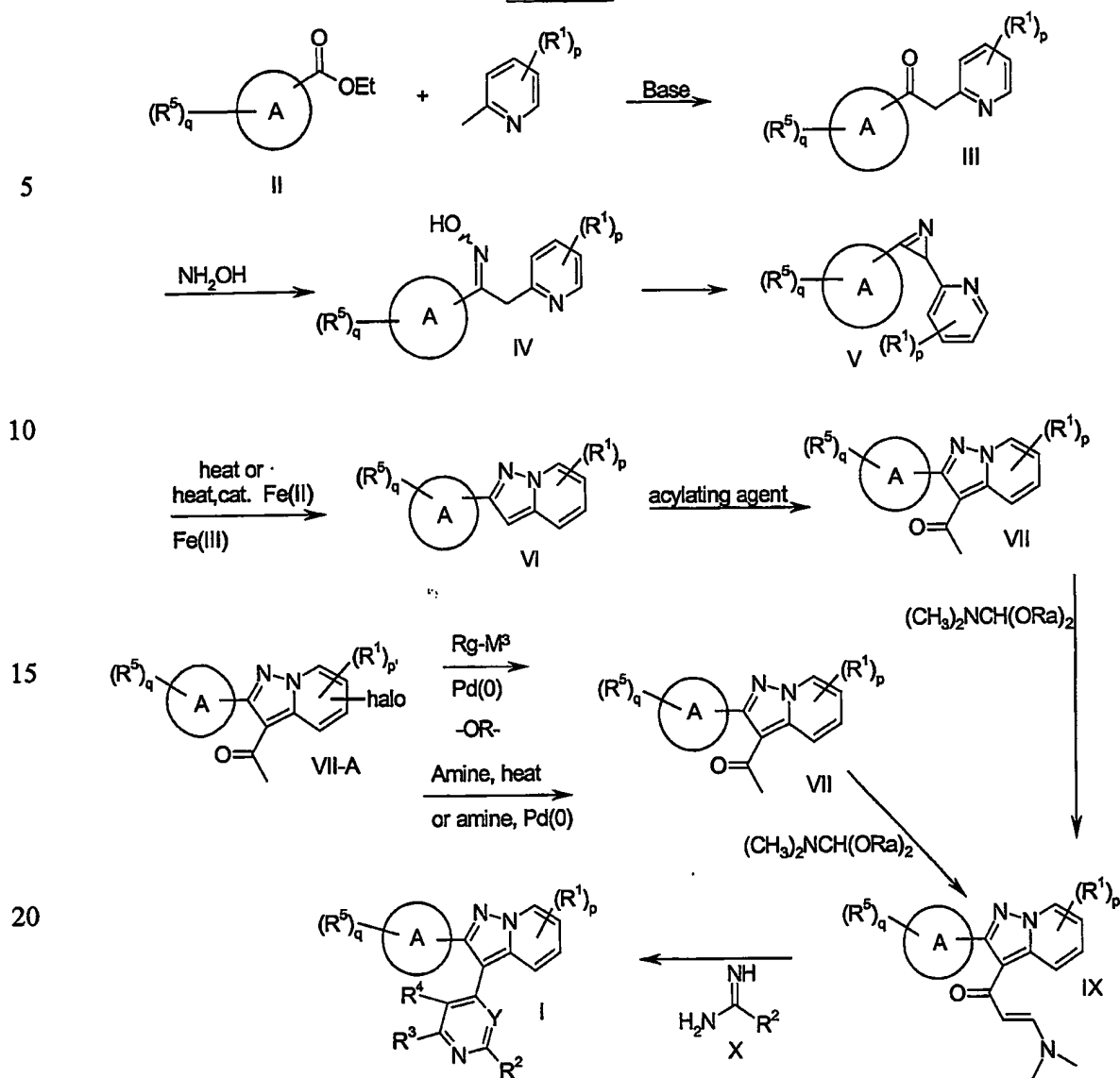
25 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optionally together with a pharmaceutically acceptable carrier or diluent comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or  
30 simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, in such a manner as  
5 are known for such compounds in the art.

When a compound of formula (I) is used in combination with a second therapeutic agent active against the viral infection, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated  
10 by those skilled in the art.

Compounds of formula (I) wherein Y is N, and R<sup>3</sup> and R<sup>4</sup> are H, may be conveniently prepared by the process outlined in Scheme 1 below.

Scheme 1



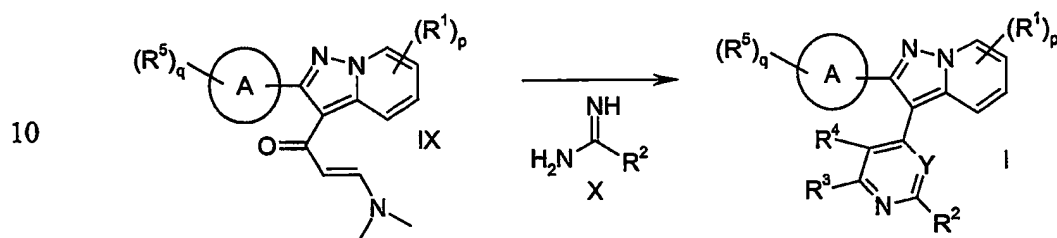
- S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,  
 -R<sup>10</sup>Ay, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)Ay, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,  
 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay,  
 -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,  
 5 -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>Ay, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and  
 azido;  
 or two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are  
 bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group  
 containing 1 or 2 heteroatoms;  
 10 each R<sup>7</sup> and R<sup>8</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  
 -C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>11</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>9</sup>R<sup>11</sup>, -SO<sub>2</sub>R<sup>10</sup>,  
 -SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 15 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;  
 each R<sup>9</sup> and R<sup>11</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, cycloalkyl, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OH,  
 -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> wherein w is 1-10, and -R<sup>10</sup>NR<sup>10</sup>R<sup>10</sup>;  
 20 each R<sup>10</sup> is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;  
 Ay is aryl;  
 Het is a 5- or 6-membered heterocyclic or heteroaryl group;  
 Y is N;  
 25 R<sup>2</sup> is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  
 Ay, Het, -OR<sup>7</sup>, -OAY, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het,  
 -S(O)<sub>n</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ay;  
 n is 0, 1 or 2;  
 R<sup>3</sup> and R<sup>4</sup> are H;  
 30 Ring A is a heterocyclic or heteroaryl group having from 5 to 10 members;  
 q is 0, 1, 2, 3, 4 or 5; and

- each  $R^5$  is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAr$ ,  $-OR^{10}Ar$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)Ar$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  
 5  $-C(NH)NR^7Ar$ ,  $-S(O)_nR^9$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ar$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}Het$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ar$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ar$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;
- 10  $R_g$  is Ay or Het as defined above;  
 $M^3$  is  $B(OH)_2$ ,  $B(ORa)_2$ ,  $B(Ra)_2$ ,  $Sn(Ra)_3$ , Zn-halide, Zn-Ra or Mg-halide; and  
 Ra is alkyl or cycloalkyl; and all other variables are defined above.
- Generally, the process for preparing the compounds of formula (I) wherein Y is N and  
 15  $R^3$  and  $R^4$  are H, (all formulas and all other variables having been defined above in connection with Scheme 1) comprises the steps of:
- (a) reacting a picoline with an ester of formula (II) to prepare a compound of formula (III);
  - (b) reacting the compound of formula (III) with a hydroxylamine source to prepare  
 20 a compound of formula (IV);
  - (c) reacting the compound of formula (IV) with an acylating or sulfonylating agent to prepare a compound of formula (V);
  - (d) rearranging the compound of formula (V) to prepare a compound of formula (VI);
  - 25 (e) acylating the compound of formula (VI) to prepare a compound of formula (VII);
  - (f) when at least one  $R^1$  is halogen (i.e., a compound of formula (VII-A)), either:
    - (1) replacing the halogen of the compound of formula (VII-A) with an amine to prepare a compound of formula (VII); or
    - 30 (2) coupling the compound of formula (VII-A) with a metal compound of formula  $R_g-M^3$  to prepare a compound of formula (VII);

- (g) reacting the compound of formula (VII) with a dimethylformamide dialkyl acetal of formula  $(\text{CH}_3)_2\text{NCH}(\text{ORa})_2$  to prepare a compound of formula (IX); and
- (h) reacting the compound of formula (IX) with a compound of formula (X) to prepare a compound of formula (I).

5

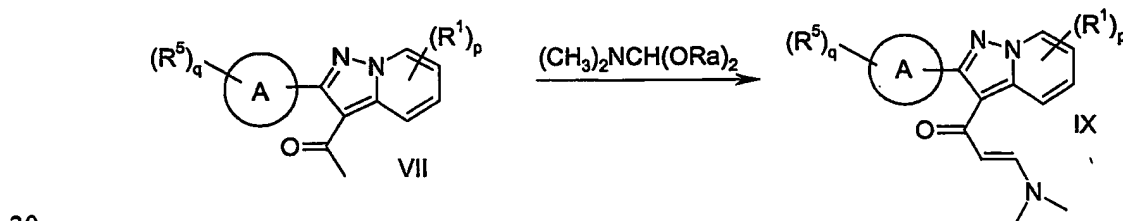
More specifically, compounds of formula (I) wherein Y is N and  $\text{R}^3$  and  $\text{R}^4$  are H can be prepared by reacting a compound of formula (IX) with a compound of formula (X).



wherein all variables are as defined above in connection with Scheme 1.

- 15 This method can be readily carried out by mixing a compound of formula (IX) with a compound of formula (X) in a suitable solvent, optionally in the presence of a base (particularly when the amidine is in a salt form), and heating the reaction to 50-150°C. Typical solvents include lower alcohols such as methanol, ethanol, isopropanol and the like and N,N-dimethylformamide. The base is typically a sodium alkoxide,
- 20 potassium carbonate, or an amine base such as triethylamine. In one embodiment, the solvent is N,N-dimethylformamide and the base is potassium carbonate, or an amine base such as triethylamine.

- Compounds of formula (IX) may be conveniently prepared by reacting a compound of
- 25 formula (VII) with a dimethylformamide dialkyl acetal, wherein  $\text{Ra}$  is alkyl or cycloalkyl.



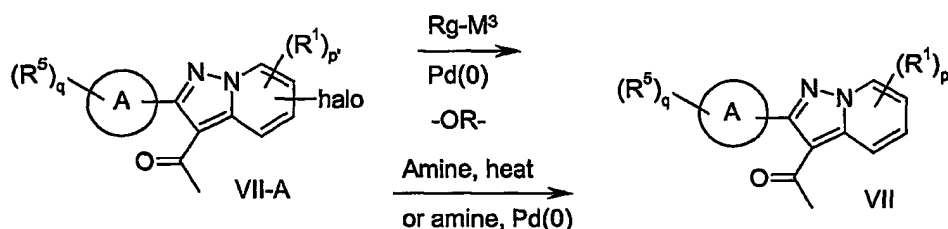
wherein all variables are as defined above in connection with Scheme 1.

Typical dimethylformamide dialkylacetal compounds for use in this method include but are not limited to dimethylformamide dimethylacetal and dimethylformamide di-*tert*-butylacetal. The reaction is carried out by mixing a compound of formula (VII) with the dimethylformamide dialkyl acetal, optionally with heating.

5

For a compound of formula (VII-A) where at least one  $R^1$  is halogen a compound of the formula (VII) may be prepared by two general methods. According to one method, a compound of formula (VII) is prepared from a compound of formula (VII-A) by replacement of the halogen with an amine nucleophile.

10



15

wherein all variables are as defined above in connection with Scheme 1.

Typically the replacement is carried out by mixing the compound of formula (VII-A) with an amine nucleophile selected from the group consisting of  $\text{-NHR}^{10}\text{Ay}$ ,  $\text{-NR}^7\text{Ay}$ , Het,  $\text{-NHHet}$ ,  $\text{-NHR}^{10}\text{Het}$  and  $\text{-NR}^7\text{R}^8$ ; and optionally heating the reaction.

20

The reaction can also be carried out via an adaptation of procedures found in the literature (Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* 2000, 65, 1144) wherein a compound of formula (VII-A) is treated with an amine, a palladium (0) or nickel (0) source and a base in a suitable solvent. Suitable sources of palladium (0) include but are not limited to palladium(II) acetate and tris(dibenzylideneacetone) dipalladium (0). Typical bases for use in the reaction include, for example sodium *tert*-butoxide and cesium carbonate. Toluene is an example of a suitable solvent.

25

According to the second method, a compound of formula (VII-A) is converted to a compound of formula (VII) by coupling with a metal compound of formula  $\text{Rg-M}^3$  wherein Rg is Ay or Het and  $\text{M}^3$  is  $\text{B(OH)}_2$ ,  $\text{B(ORa)}_2$ ,  $\text{B(Ra)}_2$ ,  $\text{Sn(Ra)}_3$ , Zn-halide; Zn-Ra or

30

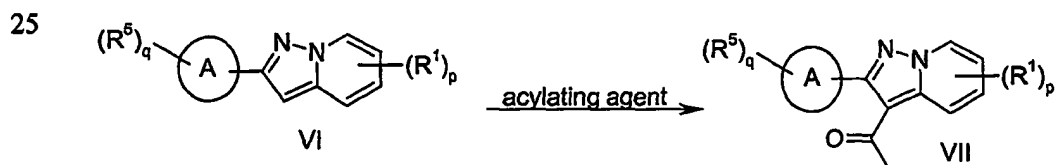
Mg-halide, wherein Ra is alkyl or cycloalkyl and halide is halo. This general method can be conveniently performed in an inert solvent, in the presence of a palladium (0) catalyst, optionally with heating. In an embodiment, the reaction is performed by reacting equimolar amounts of a compound of formula (VII-A) with the metal

5 compound of formula  $Rg-M^3$  or optionally adding an excess of the metal compound. The palladium catalyst is typically present in 1-10 mol% compared to the compound of formula (VII-A). Palladium catalysts that may be used may include, but are not limited to, tetrakis(triphenylphosphine) palladium (0) dichlorobis(triphenylphosphine)-palladium(II), and bis(diphenylphosphinoferrocene)-palladium (II) dichloride. Inert  
10 solvents for use in the reaction include but are not limited to, *N,N*-dimethylformamide, toluene, tetrahydrofuran, dioxane, and 1-methyl-2-pyrrolidinone.

When the metal compound of formula  $Rg-M^3$  is an arylboronic acid or ester or an arylborinate, the reaction is more conveniently carried out by adding a base in a  
15 proportion equivalent to, or greater than, that of the metal compound.

Metal compounds of formula  $Rg-M^3$  can be purchased from commercial sources or prepared either as discreet isolated compounds or generated *in situ* using methods known to one skilled in the art. (Suzuki, A. *J. Organomet. Chem.* 1999, 576, 147; Stille,  
20 *J. Angew. Chem. Int. Ed. Engl.* 1986, 25, 508; Snieckus, V. *J. Org. Chem.* 1995, 60, 292.)

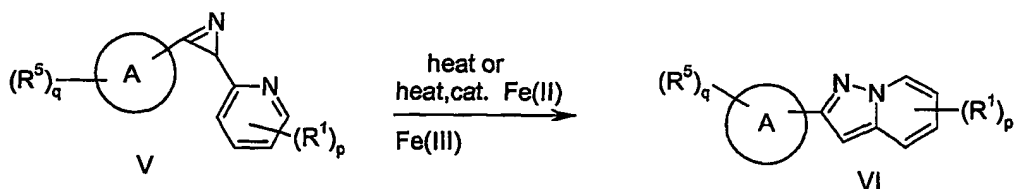
Compounds of the formula (VII) (including compounds of formula (VII-A)) may be conveniently prepared from compounds of formula (VI) using an acylation procedure.



wherein all variables are as defined above in connection with Scheme 1.

Typically the acylation is carried out by treating the compound of formula (VI) with an acylating agent, optionally in the presence of an acid or Lewis acid catalyst in an inert solvent with optional heating. Typical acylating agents will be readily determined by those skilled in the art. One particular acylating agent is acetic anhydride. Lewis acid catalysts are also known to those skilled in the art. One particular Lewis acid catalyst for use in this reaction is boron trifluoride diethyl etherate. A suitable solvent is toluene.

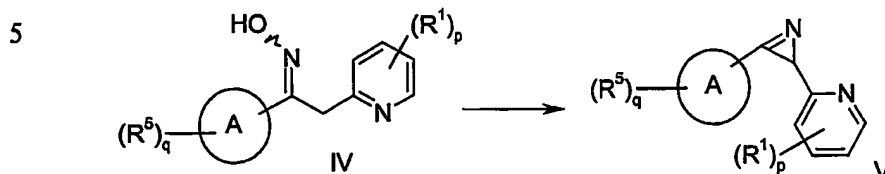
A compound of formula (VI) is conveniently prepared by rearranging an azirine compound of formula (V).



wherein all variables are as defined above in connection with Scheme 1.

The rearrangement of the azirine of formula (V) can be accomplished by heating a solution of the azirine of formula (V) in a suitable solvent at a temperature of about 160-200°C. Suitable inert solvents include, but are not limited to, 1-methyl-2-pyrrolidinone, and 1,2,4-trichlorobenzene. A particular method for rearrangement of the azirine of formula (V) to a compound of formula (VI) involves reacting the compound of formula (V) with ferrous chloride ( $\text{FeCl}_2$ ) or ferric chloride ( $\text{FeCl}_3$ ). This reaction is typically done in an inert solvent with heating. A particular solvent for this reaction is 1,2-dimethoxyethane and the like.

Typically the azirines of formula (V) are prepared from a corresponding oxime compound of formula (IV) by treatment with acylating or sulfonylating agents in the presence of a base.



wherein all variables are as defined above in connection with Scheme 1.

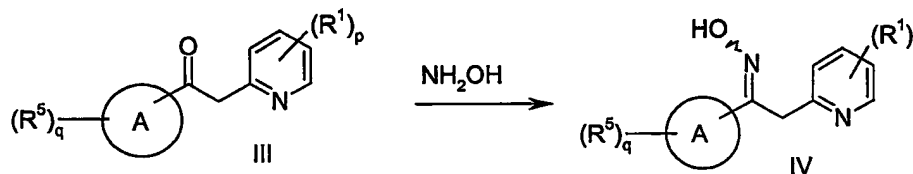
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Typical acylating or sulfonylating agents include but are not limited to, acetic anhydride, trifluoroacetic anhydride, methanesulfonyl chloride, toluenesulfonyl chloride and the like. Typical bases include, but are not limited to, triethylamine, diisopropylethylamine, pyridine, and the like. The reaction may be carried out in an inert solvent such as for example, chloroform, dichloromethane, toluene or the like.

15

The oxime compounds of formula (IV) are readily prepared by treating a ketone compound of formula (III) with a hydroxylamine source, in a suitable solvent, and optionally with a base.

20



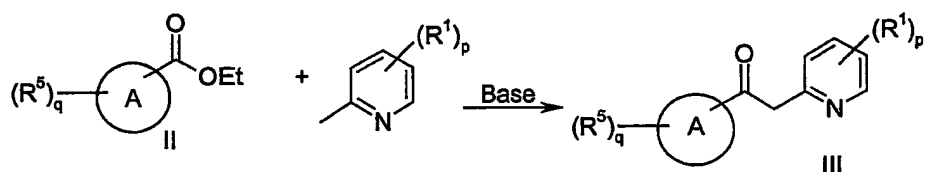
wherein all variables are as defined above in connection with Scheme 1.

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Typically the hydroxylamine is hydroxylamine hydrochloride and the base is an aqueous solution of sodium hydroxide. Suitable solvents include lower alcohols such as methanol, ethanol, or isopropanol.

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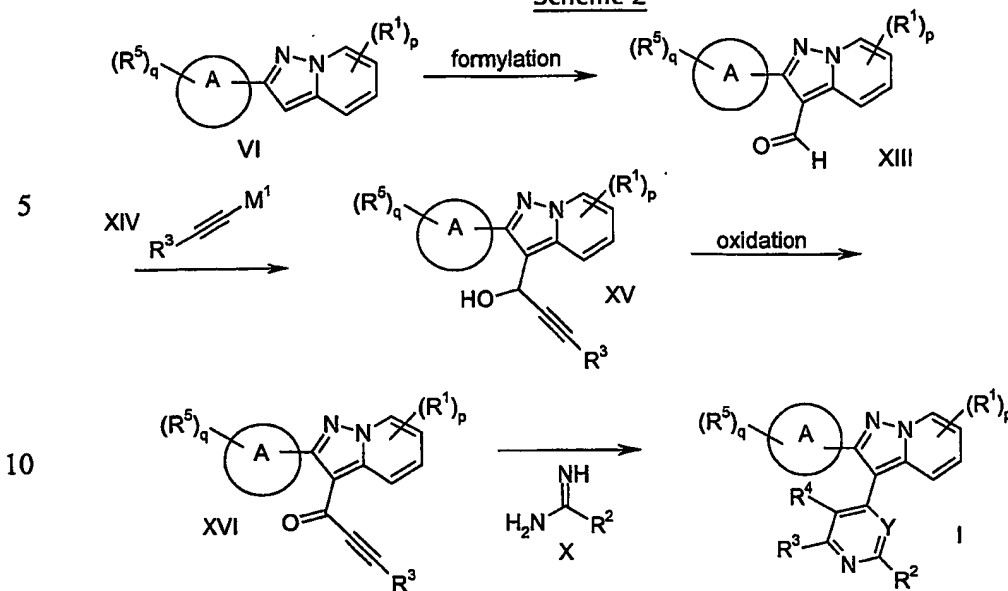
The ketone compounds of formula (III) can be prepared by treatment of a picoline with an ester of formula (II) in the presence of a base.



wherein all variables are as defined above in connection with Scheme 1.

- An example of a suitable base is lithium bis(trimethylsilyl)amide in an inert solvent such as tetrahydrofuran. Ketones such as those of formula (II) can be readily prepared using procedures known to one skilled in the art and/or described in the literature (Cassidy, R.P.; Taylor, L.T.; Wolfe, J.F. *J.Org. Chem.* 1978, 2286). Compounds of formula (II) are commercially available or can be prepared by conventional means.
- 10 In addition to the foregoing process for preparing certain compounds of formula (I), the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process. Such intermediates are described in Scheme 1 above.
- 15 In a further embodiment of the present invention, compounds of formula (I) wherein Y is N;  $R^3$  is selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, Aryl, Het,  $-OR^7$ ,  $-OAr$ ,  $-C(O)R^7$ ,  $C(O)Ar$ ,  $-CO_2R^7$ ,  $-CO_2Ar$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$  (where  $R^7$  and  $R^8$  are not H),  $-NR^7Ar$  (where  $R^7$  is not H),  $-R^{10}cycloalkyl$ ,  $-R^{10}OR^7$ ,  $-R^{10}OAr$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ar$ ; and  $R^4$  is H; and may be conveniently prepared by a process outlined in
- 20 Scheme 2 below.

Scheme 2



wherein:

p is 0, 1, 2, 3 or 4;

- 15 each  $R^1$  is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAr$ ,  $-OR^{10}Ar$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)Ar$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  $-C(NH)NR^7Ar$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAr$ ,  $-S(O)_nHet$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ar$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}Ar$ ,  $-R^{10}Het$ ,  $-R^{10}O-C(O)R^9$ ,  $-R^{10}O-C(O)Ar$ ,  $-R^{10}O-C(O)Het$ ,  $-R^{10}O-S(O)_nR^9$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ar$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ar$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;
- 20
- 25

or two adjacent  $R^1$  groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group containing 1 or 2 heteroatoms;

each  $R^7$  and  $R^8$  are the same or different and are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  $-C(O)R^9$ ,  $-CO_2R^9$ ,  $-C(O)NR^9R^{11}$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^9R^{11}$ ,  $-SO_2R^{10}$ ,

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-SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;

5 each R<sup>9</sup> and R<sup>11</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, cycloalkyl, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OH,  
 -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> wherein w is 1-10, and -R<sup>10</sup>NR<sup>10</sup>R<sup>10</sup>;

each R<sup>10</sup> is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

10 Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N;

R<sup>2</sup> is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

15 Ay, Het, -OR<sup>7</sup>, -OAy, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het,  
 -S(O)<sub>n</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and  
 -R<sup>10</sup>NR<sup>7</sup>Ay;

n is 0, 1 or 2;

20 R<sup>3</sup> is selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAy, -C(O)R<sup>7</sup>, C(O)Ay, -CO<sub>2</sub>R<sup>7</sup>, -CO<sub>2</sub>Ay, -SO<sub>2</sub>NHR<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup> (where R<sup>7</sup> and R<sup>8</sup> are  
 not H), -NR<sup>7</sup>Ay (where R<sup>7</sup> is not H), -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>7</sup>, -R<sup>10</sup>OAy, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>  
 and -R<sup>10</sup>NR<sup>7</sup>Ay;

R<sup>4</sup> is H;

Ring A is a heterocyclic or heteroaryl group having from 5 to 10 members;

q is 0, 1, 2, 3, 4 or 5;

25 each R<sup>5</sup> is the same or different and is independently selected from the group  
 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAy, -OR<sup>10</sup>Ay, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)Ay, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>,  
 -C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet,  
 30 -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>Het, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay, -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>,

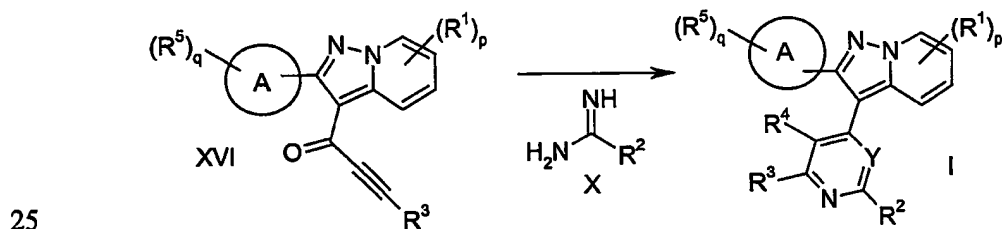
$-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  
 $-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido; and

$M^1$  is Li, Mg-halide or cerium-halide.

- 5 Generally, the process for preparing compounds of formula (I) wherein Y is N;  $R^3$  is selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$  (where  $R^7$  and  $R^8$  are not H),  $-NR^7AY$  (where  $R^7$  is not H),  $-R^{10}cycloalkyl$ ,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7AY$ ; and  $R^4$  is H; comprises the following steps:
- 10 (a) formylating a compound of formula (VI) to prepare a compound of formula (XIII);
- (b) reacting the compound of formula (XIII) with a compound of formula (XIV) to prepare a compound of formula (XV);
- (c) oxidizing the compound of formula (XV) to prepare a compound of formula
- 15 (XVI); and
- (d) reacting a compound of formula (XVI) with a compound of formula (X) to prepare a compound of formula (I).

More specifically, a compound of formula (I) may be prepared by reacting a compound

20 of formula (XVI) with a compound of formula (X).



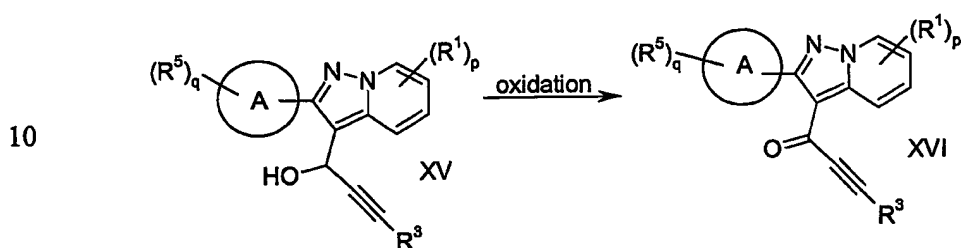
wherein all variables are as defined above in connection with Scheme 2.

- This method can be readily carried out by mixing a compound of formula (XVI) with a compound of formula (X) in a suitable solvent, optionally in the presence of a base.
- 30 The reaction may be heated to 50-150°C or performed at ambient temperature.
- Typical solvents include but are not limited to lower alcohols such as methanol,

ethanol, isopropanol and the like. Typical bases include for example, sodium alkoxide, potassium carbonate, or an amine base such as triethylamine. In another embodiment, the solvent is *N,N*-dimethylformamide and the base is potassium carbonate, or an amine base such as triethylamine.

5

A compound of formula (XVI) may be conveniently prepared by oxidation of a compound of formula (XV).

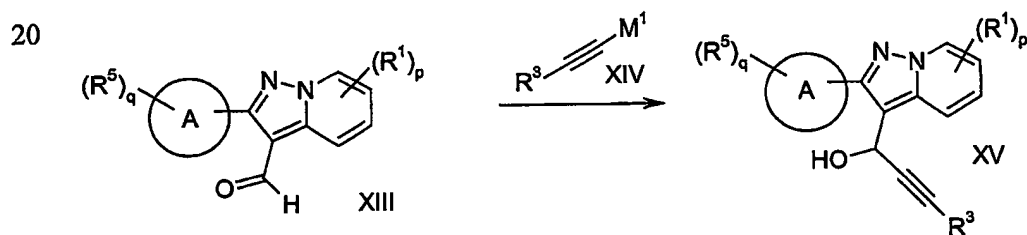


wherein all variables are as defined above in connection with Scheme 2.

Preferred oxidizing agents include but are not limited to, manganese dioxide, and the like, in an inert solvent. Suitable inert solvents include but are not limited to, dichloromethane, chloroform, *N,N*-dimethylformamide, ether, and the like.

15

A compound of formula (XV) may be conveniently prepared by reacting a compound of formula (XIII) with a compound of formula (XIV).

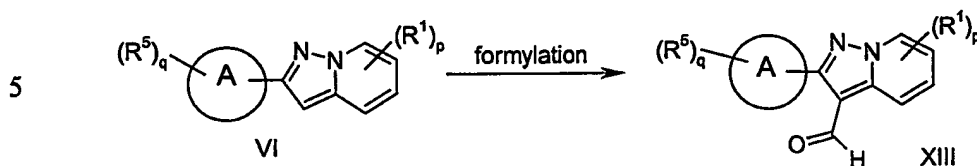


25 wherein all variables are as defined above in connection with Scheme 2.

Particular metals ( $M^1$ ) in the compounds of formula (XIV) include but are not limited to, lithium, magnesium(II) halides, cerium(III) halides, and the like. Compounds of formula (XIV) may be purchased from commercial sources or prepared by methods known to one skilled in the art.

30

Compound of formula (XIII) may be conveniently prepared from a compound of formula (VI) by a formylation procedure.



wherein all variables are as defined above in connection with Scheme 2.

10 Typically the formylation is carried out via the Vilsmeier-Haack reaction. The Vilsmeier-Haack reagents can be purchased from commercial sources or prepared *in situ*. Typical conditions include, but are not limited to treating compounds of formula (VI) with a premixed solution of phosphorous oxychloride in *N,N*-dimethylformamide optionally with heating the reaction to 50-150°C.

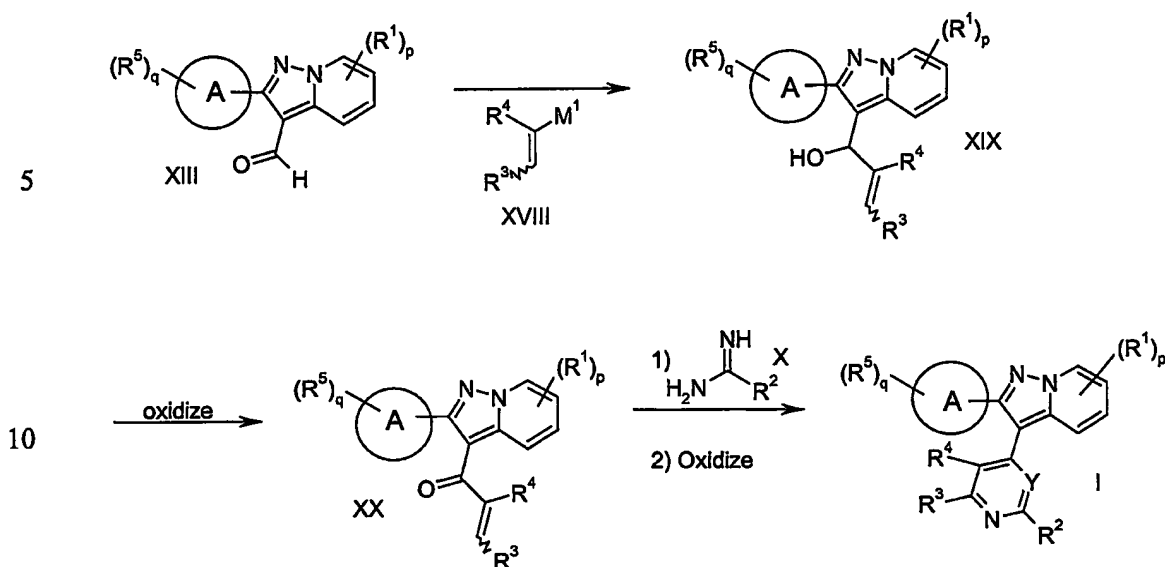
15

The compounds of formula (VI) are prepared by the process described in Scheme 1 above.

20 In addition to the foregoing process for preparing certain compounds of formula (I), the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process. Such intermediates are described in Scheme 2 above.

25 A compound of formula (I) wherein Y is N may be conveniently prepared by a process outlined in Scheme 3 below.

Scheme 3



wherein:

15  $p$  is 0, 1, 2, 3 or 4;

each  $R^1$  is the same or different and is independently selected from the group

consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  
 $-OAr$ ,  $-OR^{10}Ar$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)Ar$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  
 $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  
 $-C(NH)NR^7R^8$ ,  $-C(NH)NR^7Ar$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAr$ ,  $-S(O)_nHet$ ,  $-S(O)_2NR^7R^8$ ,  
 $-S(O)_2NR^7Ar$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  
 $-R^{10}Ar$ ,  $-R^{10}Het$ ,  $-R^{10}O-C(O)R^9$ ,  $-R^{10}O-C(O)Ar$ ,  $-R^{10}O-C(O)Het$ ,  $-R^{10}O-S(O)_nR^9$ ,  
 $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ar$ ,  
 $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  
 $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ar$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and  
25 azido;

or two adjacent  $R^1$  groups together with the carbon atoms to which they are  
bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group  
containing 1 or 2 heteroatoms;

30 each  $R^7$  and  $R^8$  are the same or different and are independently selected from  
the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

-C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>11</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>9</sup>R<sup>11</sup>, -SO<sub>2</sub>R<sup>10</sup>,  
 -SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;

each R<sup>9</sup> and R<sup>11</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, cycloalkyl, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OH,  
 -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> wherein w is 1-10, and -R<sup>10</sup>NR<sup>10</sup>R<sup>10</sup>;

each R<sup>10</sup> is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N;

R<sup>2</sup> is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

Ay, Het, -OR<sup>7</sup>, -OAY, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het,  
 -S(O)<sub>n</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ay;

n is 0, 1 or 2;

R<sup>3</sup> and R<sup>4</sup> are the same or different and are each independently selected from the  
 group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het, -OR<sup>7</sup>, -OAY,

-C(O)R<sup>7</sup>, C(O)AY, -CO<sub>2</sub>R<sup>7</sup>, -CO<sub>2</sub>AY, -SO<sub>2</sub>NHR<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet,  
 -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>7</sup>, -R<sup>10</sup>OAY, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ay;

Ring A is a 5-10 membered heterocyclic or heteroaryl group;

q is 0, 1, 2, 3, 4 or 5;

each R<sup>5</sup> is the same or different and is independently selected from the group

consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAY, -OR<sup>10</sup>Ay, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)AY, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>,  
 -C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet,  
 -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>Het, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay, -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>,  
 -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>,

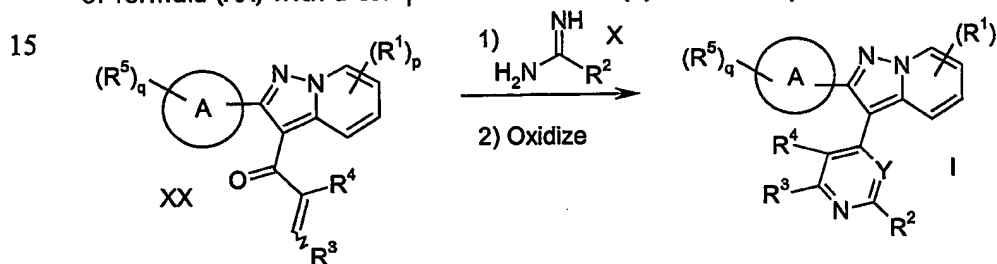
$-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido; and  $M^1$  is Li, Mg-halide or cerium-halide, wherein halide is halo.

Generally, the process for preparing compounds of formula (I) wherein Y is N

5 comprises the following steps:

- (a) reacting a compound of formula (XIII) with a compound of formula (XVIII) to prepare a compound of formula (XIX);
- (b) oxidizing the compound of formula (XIX) to prepare a compound of formula (XX); and
- 10 (c) reacting a compound of formula (XX) with a compound of formula (X) followed by oxidative aromatization to prepare a compound of formula (I).

More specifically, a compound of formula (I) can be prepared by reacting a compound of formula (XX) with a compound of formula (X) followed by oxidative aromatization.



wherein all variables are as defined above in connection with Scheme 3.

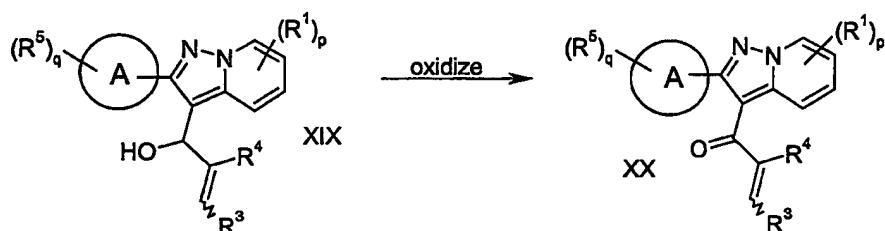
The condensation is conveniently carried out by treating the compound of formula (XX) with a compound of formula (X) in an inert solvent, optionally in the presence of a base. The reaction may be heated to 50–150°C or performed at ambient

25 temperature. Suitable inert solvents include lower alcohols such as, for example, methanol, ethanol, isopropanol and the like. The base is typically sodium alkoxide, potassium carbonate, or an amine base such as triethylamine. In another embodiment, the solvent is *N,N*-dimethylformamide and the base is potassium carbonate, or an amine base such as triethylamine. The reaction produces a

30 dihydropyrimidine intermediate.

Conveniently in the same reaction vessel, the dihydropyrimidine intermediate may be oxidized to a compound of formula (I) by the addition of an oxidizing agent. The reaction may be heated to 50-150°C or performed at ambient temperature. Typically, the oxidizing agent is oxygen (O<sub>2</sub>), palladium on carbon, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, or the like.

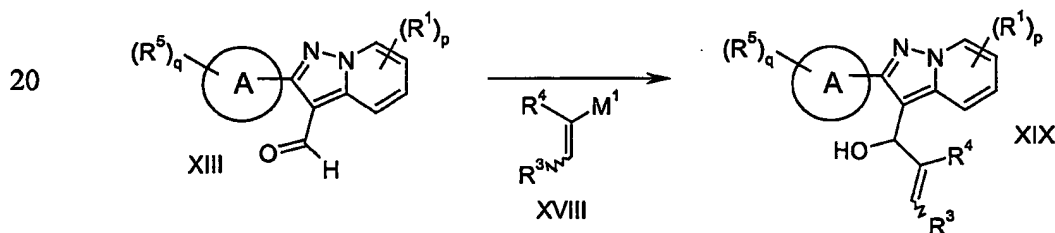
A compound of formula (XX) may be conveniently prepared by oxidation of a compound of formula (XIX).



wherein all variables are as defined above in connection with Scheme 3.

Suitable oxidizing agents for the oxidation of compounds of formula (XIX) include but are not limited to manganese dioxide, and the like. The oxidation is typically carried out in an inert solvent such as for example, dichloromethane, chloroform, *N,N*-dimethylformamide, ether, and the like.

A compound of formula (XIX) may be conveniently prepared by reacting a compound of formula (XIII) with a compound of formula (XVIII).



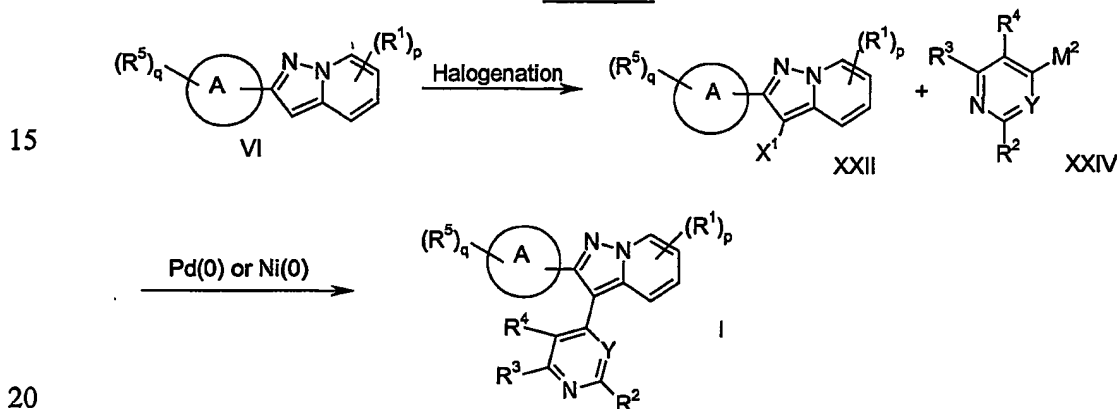
wherein M<sup>1</sup> is a metal such as for example, lithium, magnesium(II) halides, cerium(III) halides, and the like and all other variables are as defined above in connection with Scheme 3.

Compounds of formula (XVIII) may be purchased from commercial sources or prepared by methods known to one skilled in the art. The compounds of formula (XIII) may be prepared using the methods described in connection with Schemes 1 and 2 above.

- 5 In addition to the foregoing process for preparing certain compounds of formula (I), the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process. Such intermediates are described in Scheme 3 above.

- 10 A compounds of formula (I) wherein Y is CH or N, may be conveniently prepared by a process outlined in Scheme 4 below.

Scheme 4



wherein:

p is 0, 1, 2, 3 or 4;

each R<sup>1</sup> is the same or different and is independently selected from the group

- 25 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAy, -OR<sup>10</sup>Ay, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)Ay, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Ay, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>,  
 -C(NH)NR<sup>7</sup>R<sup>8</sup>, -C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>,  
 -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,  
 -R<sup>10</sup>Ay, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)Ay, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,  
 30 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay,  
 -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,

$-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

or two adjacent  $R^1$  groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group

5 containing 1 or 2 heteroatoms;

each  $R^7$  and  $R^8$  are the same or different and are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  $-C(O)R^9$ ,  $-CO_2R^9$ ,  $-C(O)NR^9R^{11}$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^9R^{11}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^9R^{11}$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^{10}$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^9R^{11}$ ,  $-R^{10}NHCOR^9$ ,  $-R^{10}NHSO_2R^9$  and  $-R^{10}NHC(NH)NR^9R^{11}$ ;

10

each  $R^9$  and  $R^{11}$  are the same or different and are independently selected from the group consisting of H, alkyl, cycloalkyl,  $-R^{10}cycloalkyl$ ,  $-R^{10}OH$ ,  $-R^{10}(OR^{10})_w$  wherein w is 1-10, and  $-R^{10}NR^{10}R^{10}$ ;

15

each  $R^{10}$  is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

20 Y is N or CH;

$R^2$  is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAy$ ,  $-S(O)_nHet$ ,  $-S(O)_nNR^7R^8$ ,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

n is 0, 1 or 2;

25  $R^3$  and  $R^4$  are the same or different and are each independently selected from the group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

Ring A is a 5-10 membered heterocyclic or heteroaryl group;

30 q is 0, 1, 2, 3, 4 or 5;

each  $R^5$  is the same or different and is independently selected from the group

- consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAr$ ,  $-OR^{10}Ar$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)Ar$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ar$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  $-C(NH)NR^7Ar$ ,  $-S(O)_nR^9$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ar$ ,  $-NR^7R^8$ ,  $-NR^7Ar$ ,  $-NHHet$ ,  $-NHR^{10}Ar$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}Het$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ar$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ar$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

$X^1$  is chloro, bromo, or iodo; and

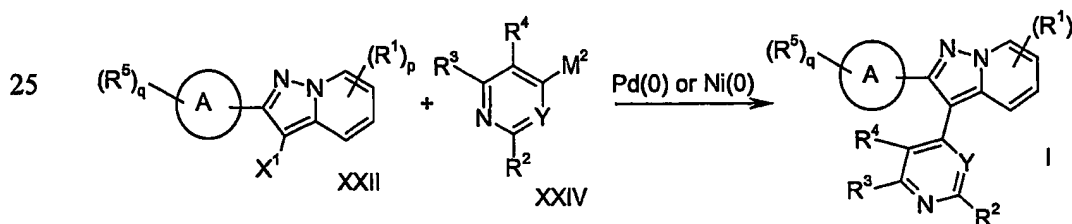
- $M^2$  is  $-B(OH)_2$ ,  $-B(ORa)_2$ ,  $-B(Ra)_2$ ,  $-Sn(Ra)_3$ , Zn-halide, ZnRa, or Mg-halide where Ra is alkyl or cycloalkyl and halide is halo.

Generally, the process for preparing compounds of formula (I) (all formulas and variables having been defined above in connection with Scheme 4), comprises the following steps:

- halogenating a compound of formula (VI) to prepare a compound of formula (XXII); and
- reacting a compound of formula (XXII) with a compound of formula (XXIV) to prepare a compound of formula (I).

20

More specifically, a compound of formula (I) wherein Y is N or CH can be prepared by reacting a compound of formula (XXII) with a compound of formula (XXIV).



wherein all variables are as defined above in connection with Scheme 4.

30

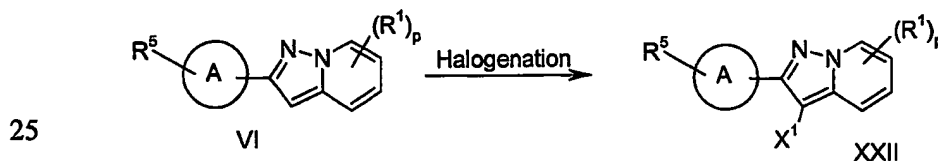
The reaction may be carried out in an inert solvent, in the presence of a palladium (0) or nickel (0) catalyst. The reaction may optionally be heated to about 50–150°C.

Typically the reaction is performed by reacting equimolar amounts of a compound of formula (XXII) with a heteroaryl-metal compound of formula (XXIV), but the reaction

- 5 may also be performed in the presence of an excess of compound of the formula (XXIV). The palladium or nickel catalyst is typically present in 1–10 mol% compared to the compound of formula (XXII). Examples of suitable palladium catalysts include but are not limited to, tetrakis(triphenylphosphine)palladium (0), dichlorobis(triphenylphosphine)palladium(II), tris(dibenzylideneacetone)dipalladium (0), and
- 10 bis(diphenylphosphinoferrocene)palladium (II) dichloride. Suitable solvents include but are not limited to, *N,N*-dimethylformamide, toluene, tetrahydrofuran, dioxane, and 1-methyl-2-pyrrolidinone. When the heteroaryl-metal compound of formula (XXIV) is an arylboronic acid or ester or an arylborinate the reaction is more conveniently carried out by adding a base in a proportion equivalent to, or greater
- 15 than, that of the compound of formula (XXIV). Heteroaryl-metal compounds of formula (XXIV) may be obtained from commercial sources or prepared either as discreet isolated compounds or generated *in situ* using methods known to one skilled in the art. (Suzuki, A. *J. Organomet. Chem.* 1999, 576, 147; Stille, J. *Angew. Chem. Int. Ed. Engl.* 1986, 25, 508; Snieckus, V. *J. Org. Chem.* 1995, 60, 292.)

20

A compound of formula (XXII) can be prepared from a compound of formula (VI) by a halogenation procedure.

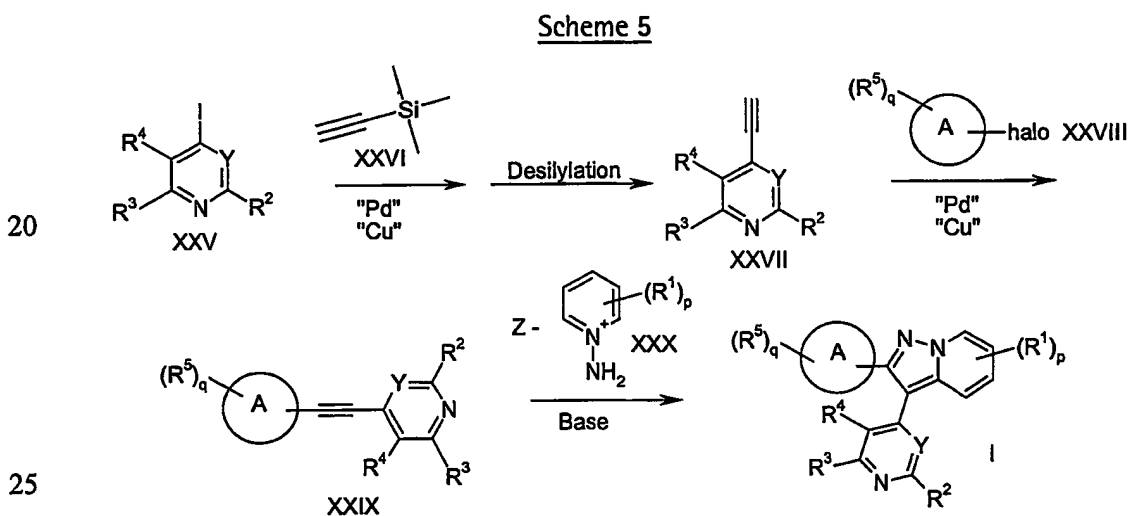


wherein all variables are as defined above in connection with Scheme 4.

Typically, the halogenation reaction is carried out by subjecting the compound of formula (VI) to a halogenating agent in a suitable solvent. Suitable halogenating agents include but are not limited to, iodine, *N*-bromosuccinimide, trialkylammonium tribromides, bromine, *N*-chlorosuccinimide, *N*-iodosuccinimide, iodine, iodine  
 5 monochloride, and the like. Suitable solvents include, for example, *N,N*-dimethylformamide, tetrahydrofuran, dioxane, 1-methyl-2-pyrrolidinone, carbon tetrachloride, toluene, dichloromethane, diethyl ether, and the like.

In addition to the foregoing process for preparing certain compounds of formula (I),  
 10 the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process. Such intermediates are described in Scheme 4 above.

In another embodiment, a compound of formula (I) may be conveniently prepared by  
 15 a process outlined in Scheme 5 below



wherein:

*p* is 0, 1, 2, 3 or 4;

each *R*<sup>1</sup> is the same or different and is independently selected from the group

30 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAr, -OR<sup>10</sup>Ar, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)Ar, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,

-C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Ay, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>,  
 -C(NH)NR<sup>7</sup>R<sup>8</sup>, -C(NH)NR<sup>7</sup>Ay, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>,  
 -S(O)<sub>2</sub>NR<sup>7</sup>Ay, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,  
 -R<sup>10</sup>Ay, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)Ay, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,  
 5 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>Ay,  
 -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>Ay, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and  
 azido;

or two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are  
 10 bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group  
 containing 1 or 2 heteroatoms;

each R<sup>7</sup> and R<sup>8</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  
 -C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>11</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>9</sup>R<sup>11</sup>, -SO<sub>2</sub>R<sup>10</sup>,  
 15 -SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;

each R<sup>9</sup> and R<sup>11</sup> are the same or different and are independently selected from  
 20 the group consisting of H, alkyl, cycloalkyl, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OH,  
 -R<sup>10</sup>(OR<sup>10</sup>)<sub>w</sub> wherein w is 1-10, and -R<sup>10</sup>NR<sup>10</sup>R<sup>10</sup>;

each R<sup>10</sup> is the same or different and is independently selected from the group  
 consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

Ay is aryl;

25 Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N or CH;

R<sup>2</sup> is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

Ay, Het, -OR<sup>7</sup>, -OAy, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>Ay, -S(O)<sub>n</sub>Het,  
 -S(O)<sub>n</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and  
 30 -R<sup>10</sup>NR<sup>7</sup>Ay;

n is 0, 1 or 2;

$R^3$  and  $R^4$  are the same or different and are each independently selected from the group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$ ,  $-NR^7AY$ ,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7AY$ ;

5 Ring A is a 5-10 membered heterocyclic or heteroaryl group;

q is 0, 1, 2, 3, 4 or 5;

each  $R^5$  is the same or different and is independently selected from the group

consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OR^{10}AY$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)AY$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  
 10  $-C(O)NR^7R^8$ ,  $-C(O)NR^7AY$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  
 $-C(NH)NR^7AY$ ,  $-S(O)_nR^9$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7AY$ ,  $-NR^7R^8$ ,  $-NR^7AY$ ,  $-NHHet$ ,  
 $-NHR^{10}AY$ ,  $-NHR^{10}Het$ ,  $-R^{10}cycloalkyl$ ,  $-R^{10}Het$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  
 $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7AY$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  
 $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  
 15  $-R^{10}NR^7AY$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido; and

$Z^-$  is a counter ion.

Generally, a compound of formula (I) may be prepared by a process comprising the steps of:

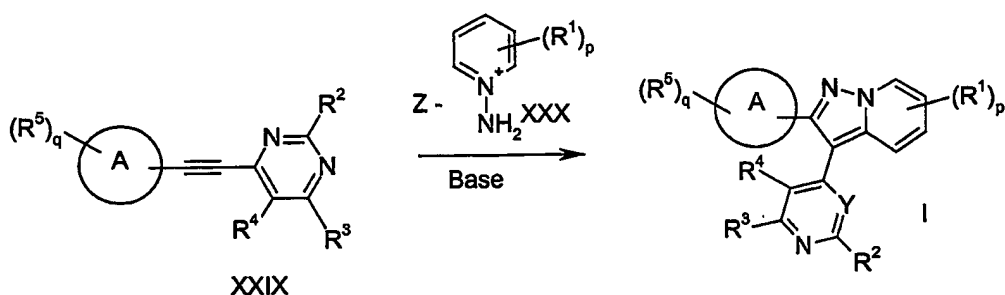
- (a) reacting a compound of formula (XXV) with an alkyne of formula (XXVI)
- 20 followed by desilylation to give a compound of formula (XXVII);
- (b) reacting the compound of formula (XXVII) with a compound of formula (XXVIII) to prepare a compound of formula (XXIX);
- (c) reacting the compound of formula (XXIX) with a 1-aminopyridinium salt of formula (XXX) to prepare a compound of formula (I).

25

The order of the foregoing steps is not critical to the process and as such these steps may be carried out in any suitable order according to the skill in the art.

More specifically, a compound of formula (I) can be prepared by reacting a compound of formula (XXIX) with a 1-aminopyridinium salt of formula (XXX) to prepare a

30 compound of formula (I).



wherein all variables are as defined above in connection with Scheme 5.

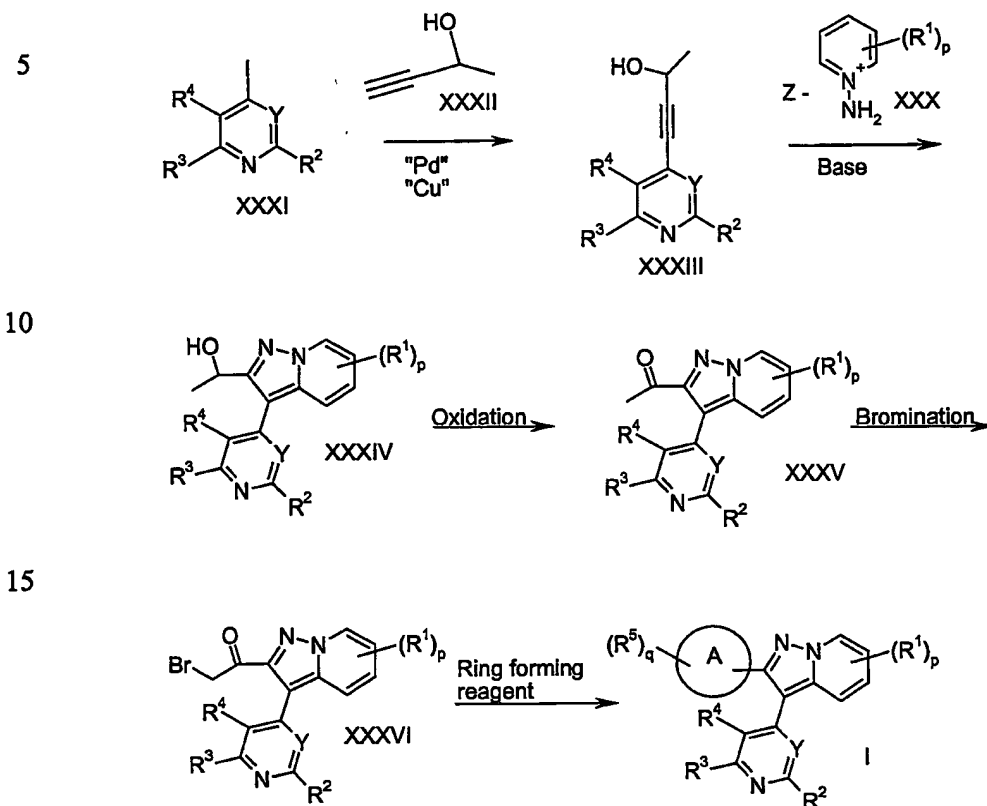
Cycloaddition reactions such as these are commonly known as [3+2] dipolar  
 5 cycloaddition reactions. Conveniently the reaction may be carried out by mixing the reactants (i.e., compounds of formula (XXVII) and (XXVIII)), in equimolar amounts, in an inert solvent and adding a suitable base. The mixture is then stirred at between 20-100°C until the reaction is judged complete by the disappearance of one of the reactants. Suitable solvents include but are not limited to acetonitrile, dioxane,  
 10 tetrahydrofuran, dimethylformamide and the like. Suitable bases include non-nucleophilic amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane and the like. Compounds of formula (XXX) are aminated pyridine derivatives and are either commercially available or can be conveniently prepared by reacting a suitable pyridine  
 15 with an aminating reagent such as O-(mesitylsulfonyl)hydroxylamine, O-(diphenylphosphinyl)hydroxylamine, hydroxylamine-O-sulfonic acid and the like.

Alkynyl compounds of formula (XXIX) are either known compounds or can be prepared  
 20 by methods described in the literature or known to those skilled in the art of organic synthesis.

In addition to the foregoing process for preparing certain compounds of formula (I), the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process.  
 25 Such intermediates are described in Scheme 5 above.

In a further embodiment, a compound of formula (I) may be conveniently prepared by a process outlined in Scheme 6 below

Scheme 6



wherein:

p is 0, 1, 2, 3 or 4;

each R<sup>1</sup> is the same or different and is independently selected from the group

consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,

25 -OAY, -OR<sup>10</sup>AY, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)AY, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,

-C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>AY, -C(O)NHR<sup>10</sup>AY, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>,

-C(NH)NR<sup>7</sup>R<sup>8</sup>, -C(NH)NR<sup>7</sup>AY, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>AY, -S(O)<sub>n</sub>Het, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>,

-S(O)<sub>2</sub>NR<sup>7</sup>AY, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>AY, -NHHet, -NHR<sup>10</sup>AY, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,

-R<sup>10</sup>AY, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)AY, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,

30 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>AY,

-R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,

$-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

or two adjacent  $R^1$  groups together with the carbon atoms to which they are bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group  
 5 containing 1 or 2 heteroatoms;

each  $R^7$  and  $R^8$  are the same or different and are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  $-C(O)R^9$ ,  $-CO_2R^9$ ,  $-C(O)NR^9R^{11}$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^9R^{11}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^9R^{11}$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  
 10  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^{10}$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^9R^{11}$ ,  $-R^{10}NHCOR^9$ ,  $-R^{10}NHSO_2R^9$  and  $-R^{10}NHC(NH)NR^9R^{11}$ ;

each  $R^9$  and  $R^{11}$  are the same or different and are independently selected from the group consisting of H, alkyl, cycloalkyl,  $-R^{10}$ cycloalkyl,  $-R^{10}OH$ ,  
 15  $-R^{10}(OR^{10})_w$  wherein w is 1-10, and  $-R^{10}NR^{10}R^{10}$ ;

each  $R^{10}$  is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

20 Y is N or CH;

$R^2$  is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-S(O)_nR^8$ ,  $-S(O)_nAy$ ,  $-S(O)_nHet$ ,  $-S(O)_nNR^7R^8$ ,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

25 n is 0, 1 or 2;

$R^3$  and  $R^4$  are the same or different and are each independently selected from the group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

30 Ring A is a 5-10 membered heterocyclic or heteroaryl group;

q is 0, 1, 2, 3, 4 or 5;

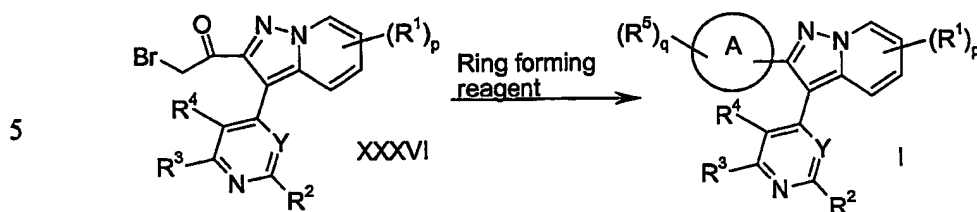
each R<sup>5</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>, -OAY, -OR<sup>10</sup>AY, -OHet, -OR<sup>10</sup>Het, , -C(O)R<sup>9</sup>, -C(O)AY, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>AY, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>7</sup>R<sup>8</sup>,  
 5 -C(NH)NR<sup>7</sup>AY, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>7</sup>AY, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>AY, -NHHet, -NHR<sup>10</sup>AY, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>Het, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>AY, -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCO<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>AY, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and azido; and

10 Z- is a counter ion.

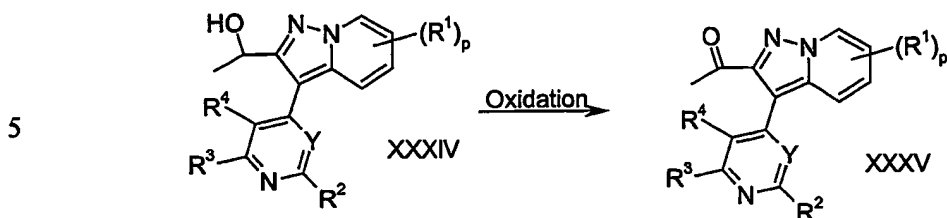
Generally, a compound of formula (I) can be prepared by a process comprising the steps of:

- (a) reacting a compound of formula (XXXI) with an alkyne of formula (XXXII) to  
 15 prepare a compound of formula (XXXIII);
- (b) reacting the compound of formula (XXXIII) with a 1-aminopyridinium salt of formula (XXX) to prepare a compound of formula (XXXIV);
- (c) oxidizing the compound of formula (XXXIV) to prepare a compound of formula (XXXV);
- 20 (d) brominating the compound of formula (XXXV) to prepare a compound of formula (XXXVI); and
- (e) treating the compound of formula (XXXVI) with a ring forming reagent to prepare a compound of formula (I).

More specifically, a compound of formula (I) can be prepared by reacting the compound of formula (XXXVI) with a suitable ring forming reagent.



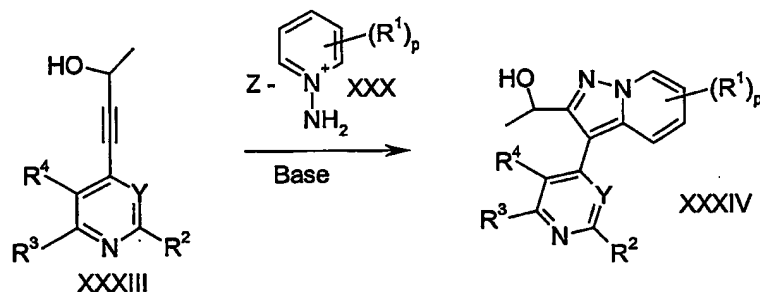
A compound of formula (XXXV) can be prepared by oxidation of a compound of formula (XXXIV).



wherein all variables are as defined above in connection with Scheme 6.

- 10 Suitable oxidizing agents include but are not limited to, manganese dioxide, and the like, in an inert solvent. Suitable inert solvents include but are not limited to, dichloromethane, chloroform, *N,N*-dimethylformamide, ether, and the like.

- 15 A compound of formula (XXXIV) can be prepared by reacting a compound of formula (XXXIII) with a 1-aminopyridinium salt of formula (XXX).



wherein all variables are as defined above in connection with Scheme 6.

- 20 Cycloaddition reactions such as these are commonly known as [3+2] dipolar cycloaddition reactions. Conveniently the reaction may be carried out by mixing the reactants (XXXIII) and (XXX), in equimolar amounts, in an inert solvent and adding a suitable base. The mixture is then stirred at between 20-100°C until the reaction is judged complete by the disappearance of one of the reactants. Suitable solvents include but are not limited to acetonitrile, dioxane, tetrahydrofuran,
- 25 dimethylformamide and the like. Suitable bases include non-nucleophilic amines such

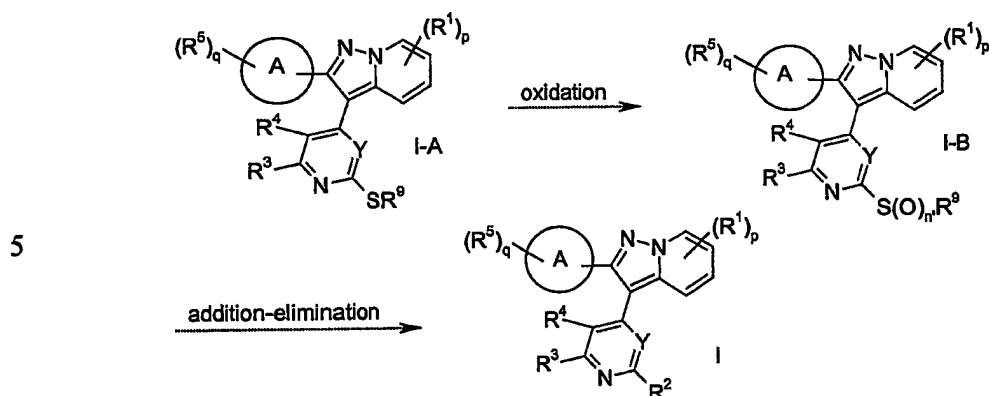
as 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane and the like.

Acetylenic compounds of formula (XXXIII) are either known compounds or can be prepared by methods described in the literature or are known to those skilled in the art of organic synthesis.

In addition to the foregoing process for preparing certain compounds of formula (I), the present invention also provides certain intermediate compounds for use in the preparation of such compounds of formula (I) according to the foregoing process. Such intermediates are described in Scheme 6 above.

Any of the processes described above may optionally comprise the further step of converting a compound of formula (I) into a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. Processes for such conversion are well known in the art.

As will be apparent to those skilled in the art, the compounds of formula (I) may be converted to other compounds of formula (I) using techniques well known in the art. For example, one method of converting a compound of formula (I) to another compound of formula (I) comprises a) oxidizing the compound of formula (I-A) to prepare a compound of formula (I-B) and then b) optionally reacting a compound of formula (I-B) with an oxygen or amine nucleophile of formula  $R^2$ , wherein  $R^2$  is  $-NR^7R^8$ ,  $-OR^7$ , Het attached through N,  $-NHHet$ ,  $NHR^{10}Het$ ,  $OHet$  and  $-OR^{10}Het$  to produce a compound of formula (I) wherein  $R^2$  is  $-NR^7R^8$ ,  $-OR^7$ , Het attached through N,  $-NHHet$ ,  $NHR^{10}Het$ ,  $OHet$  and  $-OR^{10}Het$ .



10 wherein  $n'$  is 1 or 2;

$R^2$  is selected from the group consisting of  $-\text{NR}^7\text{R}^8$ ,  $-\text{OR}^7$ , Het linked through N,  $-\text{NHHet}$ ,  $-\text{NHR}^{10}\text{Het}$ ,  $-\text{OHet}$ , and  $-\text{OR}^{10}\text{Het}$ ; and all other variables are as defined according to any process described above.

15 More specifically, a compound of formula (I) wherein  $R^2$  is selected from the group consisting of  $-\text{NR}^7\text{R}^8$ ,  $-\text{OR}^7$ , Het linked through N,  $-\text{NHHet}$ ,  $-\text{NHR}^{10}\text{Het}$ ,  $-\text{OHet}$ , and  $-\text{OR}^{10}\text{Het}$ , can be prepared by reacting a compound of formula (I-B) (i.e., a compound of formula (I) wherein  $R^2$  is  $-\text{S(O)}_{n'}\text{R}^8$  where  $n'$  is 1 or 2) with an oxygen or amine nucleophile of formula  $R^2$ , wherein  $R^2$  is  $-\text{NR}^7\text{R}^8$ ,  $-\text{OR}^7$ , Het linked through N,  $-\text{NHHet}$ ,  $-\text{NHR}^{10}\text{Het}$ ,  $-\text{OHet}$ , and  $-\text{OR}^{10}\text{Het}$ . The reaction may be carried out neat or in a suitable solvent and may be heated to 50-150°C. Typically the solvent is a lower alcohol such as methanol, ethanol, isopropanol and the like or solvent such as *N,N*-dimethylformamide or tetrahydrofuran, and the like. Optionally a base may be used to facilitate the reaction. Typically the base can be potassium carbonate, or an amine base such as triethylamine.

25

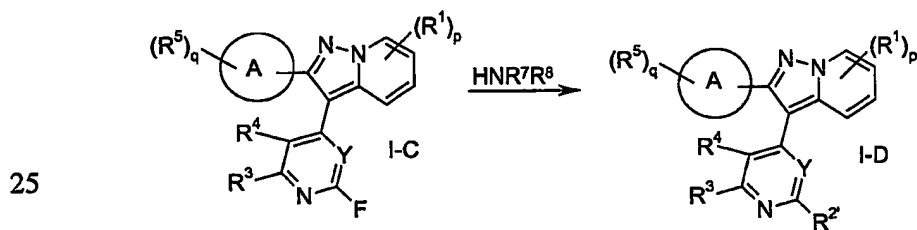
A compound of formula (I-B) may be conveniently prepared by reacting a compound of formula (I-A) (i.e., a compound of formula (I) wherein  $R^2$  is  $-\text{S(O)}_n\text{R}^8$  where  $n$  is 0) with an oxidizing agent in an inert solvent, optionally in the presence of a base.

30 Typically the oxidizing agent is a peracid such as 3-chloroperbenzoic acid or the like optionally with a base such as sodium bicarbonate. Careful monitoring of the

stoichiometry between the oxidizing agent and the substrate allows the product distribution between sulfoxide ( $n=1$ ), and sulfone ( $n=2$ ) to be controlled. Suitable solvents include but are not limited to, dichloromethane, chloroform and the like. If the compound of formula (I-A) contains oxidizable nitrogens, it may be preferred to perform the oxidation under acidic conditions. Acetic acid and the like can be added to make the solution acidic.

A compound of formula (I-A) can be prepared by methods described above wherein  $R^2=SR^9$  from the reaction of a compound selected from the group consisting of a compound of formula (XVI), a compound of formula (IX) and a compound of formula (XX) with a compound of formula (X-A) (i.e., the compound of formula (X) wherein  $R^2$  is  $-SR^9$ ). The requisite compound of formula (X-A) can be obtained from commercial sources or prepared by methods known to one skilled in the art.

Another particularly useful method for converting a compound of formula (I) to another compound of formula (I) comprises reacting a compound of formula (I-C) (i.e., a compound of formula (I) wherein  $R^2$  is fluoro) with an amine nucleophile (including unsubstituted and substituted amines, heterocycles and heteroaryls, particularly those bound through N), and optionally heating the mixture to 50–150°C to prepare a compound of formula (I-D) (i.e., a compound of formula (I) wherein  $R^2$  is selected from the group consisting of Het,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$  and  $-NHR^{10}Het$ ).



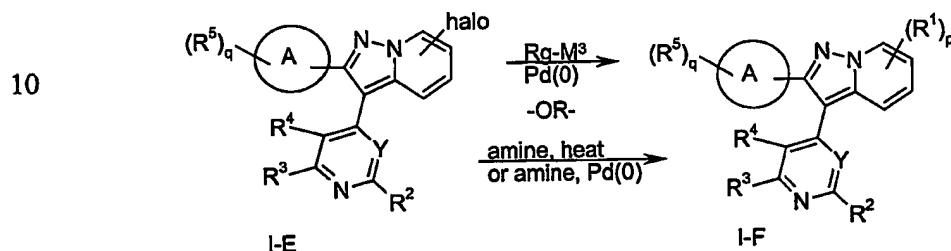
wherein  $R^2$  is selected from the group consisting of Het,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$  and  $-NHR^{10}Het$ , and

all other variables are as defined in any process described above.

30

This procedure may be carried out by mixing a compound of formula (I-C) in a neat amine, or in a suitable solvent with an excess of an amine to produce a compound of formula (I-D). Typically the solvent is a lower alcohol such as methanol, ethanol, isopropanol and the like. Other suitable solvents may include *N,N*-  
 5 dimethylformamide, 1-methyl-2-pyrrolidine and the like.

As a further example, a compound of formula (I-E) may be converted to a compound of formula (I-F) using either of two methods.

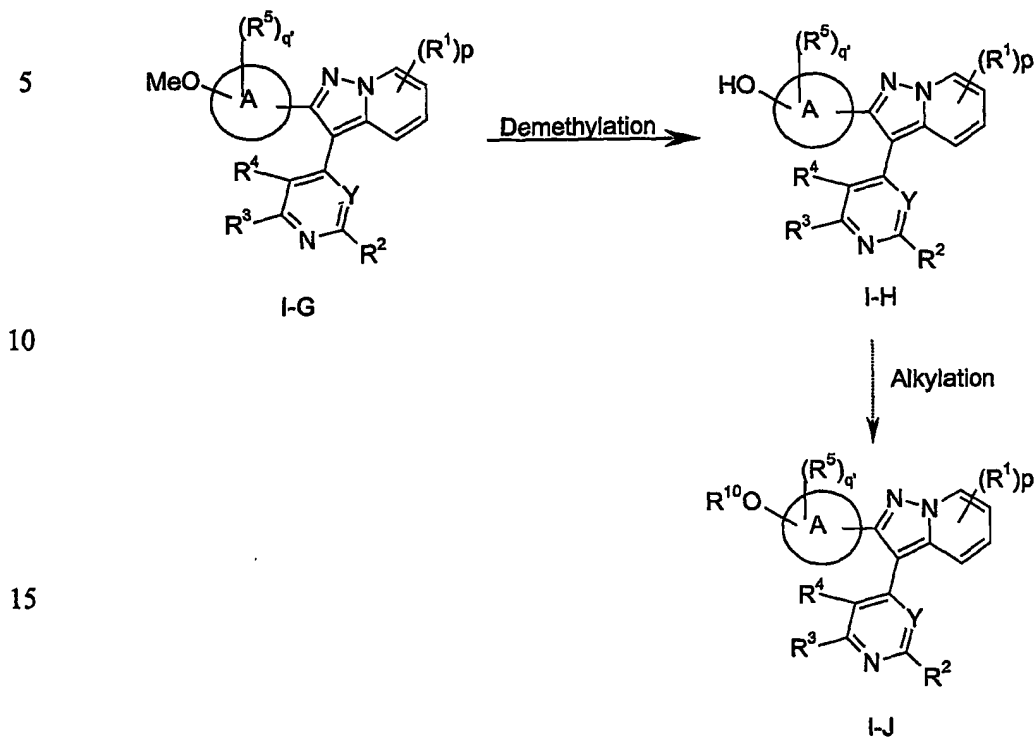


15 wherein  $M^3$  is  $B(OH)_2$ ,  $B(ORa)_2$ ,  $B(Ra)_2$ ,  $Sn(Ra)_3$ , Zn-halide; Zn-Ra or Mg-halide, Rg is Ar or Het, and all other variables are as defined in any process described above.

Such method can be carried out using the reaction and conditions described above in connection with Scheme 1 for the conversion of a compound of formula (VII-A) to a  
 20 compound of formula (VII). Thus, the present invention provides a process for converting a compound of formula (I-E) to a compound of formula (I-F) which comprises either: (1) replacing a halogen of the compound of formula (I-E) with an amine; or (2) coupling the compound of formula (I-E) with a metal compound of the formula  $Rg-M^3$  where  $M^3$  is  $B(OH)_2$ ,  $B(ORa)_2$ ,  $B(Ra)_2$ ,  $Sn(Ra)_3$ , Zn-halide; Zn-Ra or Mg-  
 25 halide.

As a further example, a compound of formula (I-G) (i.e., a compound of formula (I) wherein q is 1 or more and at least one  $R^5$  is -O-methyl) may be converted to a compound of formula (I-H) (i.e., a compound of formula (I) wherein q is 1 or more and  
 30 at least one  $R^5$  is -OH) using conventional demethylation techniques. Additionally, a compound of formula (I-H) may optionally be converted to a compound of formula

(I-J) (i.e., a compound of formula (I) wherein q is 1 or more and at least one R<sup>5</sup> is -OR<sup>10</sup>). For example, the foregoing conversions are represented schematically as follows:



20 wherein q' is 0-4; Me is methyl and all other variables are defined according to any process described above.

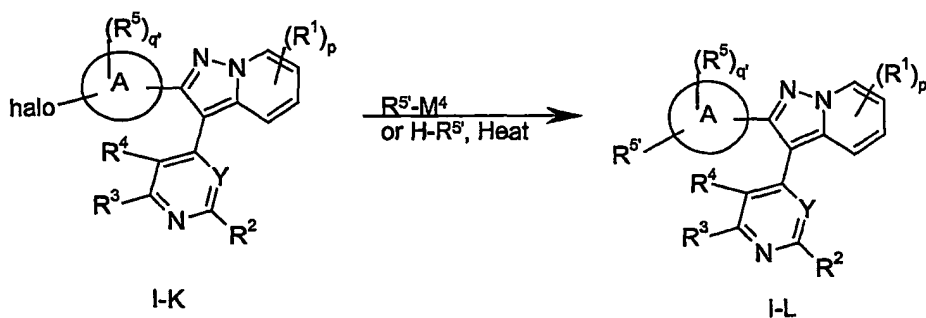
25 The demethylation reaction may be carried out by treating a compound of formula (I-G) in a suitable solvent with a Lewis acid at a temperature of -78°C to room temperature, to produce a compound of formula (I-H). Typically the solvent is an inert solvent such as dichloromethane, chloroform, acetonitrile, toluene or the like. The Lewis acid may be boron tribromide, trimethylsilyl iodide or the like.

30 Optionally, a compound of formula (I-H) may be further converted to a compound of formula (I-J) by an alkylation reaction. The alkylation reaction may be carried out by treating a compound of formula (I-H) in suitable solvent with an alkyl halide of formula R<sup>10</sup>-halo where R<sup>10</sup> is as defined above, to form another compound of formula

(I-J). The reaction is preferably carried out in the presence of a base and with optionally heating to 50–200°C. The reaction may be carried out in solvents such as N,N-dimethylformamide, dimethylsulfoxide and the like. Typically the base is potassium carbonate, cesium carbonate, sodium hydride or the like. Additionally, as  
 5 will be apparent to those skilled in the art, the alkylation reaction can be carried out under Mitsunobu conditions.

The foregoing reaction method can also be used to convert a compound of formula (I) wherein at least one R<sup>1</sup> is –OMe to a compound of formula (I) wherein at least one R<sup>1</sup>  
 10 is –OR<sup>10</sup>. In another embodiment, the foregoing methods are employed to make the same conversion when R<sup>3</sup> or R<sup>4</sup> is –OMe, to prepare a compound of formula (I) wherein R<sup>3</sup> or R<sup>4</sup> is –OH or a compound of formula (I) wherein R<sup>3</sup> or R<sup>4</sup> is –OR<sup>10</sup>.

As a further example of methods for converting a compound of formula (I) to another  
 15 compound of formula (I), a compound of formula (I-K) (i.e., a compound of formula (I) wherein q is 1 or more and at least one R<sup>5</sup> is halo) may be converted to a compound of formula (I-L) (i.e., a compound of formula (I) wherein q is 1 or more and at least one R<sup>5</sup> is Ay, Het or a nitrogen-linked substituent). For example, the conversion of a compound of formula (I-K) to a compound of formula (I-L) is shown schematically  
 20 below.



wherein:

q' is 0–4;

R<sup>5</sup> is selected from the group consisting of Ay, –NHR<sup>10</sup>Ay, –NR<sup>7</sup>Ay, Het, –NHHet,

–NHR<sup>10</sup>Het, and –NR<sup>7</sup>R<sup>8</sup>;

M<sup>4</sup> is selected from the group consisting of -B(OH)<sub>2</sub>, -B(ORa)<sub>2</sub>, -B(Ra)<sub>2</sub>, and -Sn(Ra)<sub>2</sub>

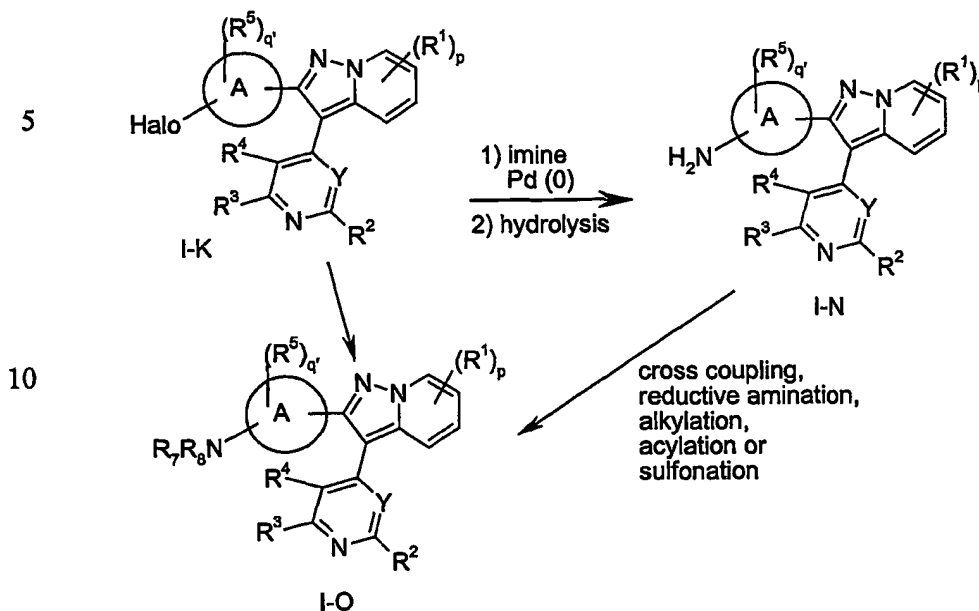
wherein Ra is alkyl or cycloalkyl; and

all other variables are as defined according to any process described above.

- 5 The conversion of compounds of formula (I-K) to compounds of formula (I-L) is carried out by heating with a compound of formula H-R<sup>5</sup> or coupling the compound of formula (I-K) with a compound of formula R<sup>5</sup>-M<sup>4</sup>, where M<sup>4</sup> is -B(OH)<sub>2</sub>, -B(ORa)<sub>2</sub>, -B(Ra)<sub>2</sub>, -Sn(Ra)<sub>2</sub> wherein Ra is alkyl or cycloalkyl. The reaction may be carried out in an inert solvent, in the presence of a palladium (0) source. The reaction may
- 10 optionally be heated to 50-150°C. Preferably the reaction is performed by reacting equimolar amounts of a compound of formula (I-K) with a compound of formula R<sup>5</sup>-M<sup>4</sup>. The reaction may also be performed in the presence of an excess R<sup>5</sup>-M<sup>4</sup>. The palladium (0) catalyst is preferably present in 1-25 mol% compared to the compound of formula (I-K). Examples of suitable palladium catalysts include but are not limited
- 15 to, tetrakis(triphenylphosphine)palladium (0), dichlorobis(triphenylphosphine)-palladium(II), and bis(diphenylphosphinoferrocene)palladium (II) dichloride. Suitable solvents include but are not limited to, N,N-dimethylformamide, toluene, tetrahydrofuran, dioxane, and 1-methyl-2-pyrrolidinone. When the compound of formula R<sup>5</sup>-M<sup>4</sup> is a boronic acid or ester or a borinate the reaction is more
- 20 conveniently carried out by adding a base in a proportion equivalent to, or greater than, that of the compound of formula R<sup>5</sup>-M<sup>4</sup>. A compound of formula R<sup>5</sup>-M<sup>4</sup> may be obtained from commercial sources or prepared either as discrete isolated compound or generated *in situ* using methods known to one skilled in the art. (Suzuki, A. J. *Organomet. Chem.* 1999, 576, 147; Stille, J. *Angew. Chem. Int. Ed. Engl.* 1986, 25,
- 25 508; Snieckus, V. *J. Org. Chem.* 1995, 60, 292.)

- In yet another example, a compound of formula (I-K) (i.e., a compound of formula (I) wherein q is 1 or more and at least one R<sup>5</sup> is halo) is converted to a compound of formula (I-N) (i.e., a compound of formula (I) wherein q is 1 or more and at least one
- 30 R<sup>5</sup> is -NH<sub>2</sub>). Optionally, a compound of formula (I-N) may then be converted to a compound of formula (I-O) (i.e., a compound of formula (I) wherein q is 1 or more and

at least one  $R^5$  is  $-NR^7R^8$  where  $R^7$  and  $R^8$  are not both H). For example, the foregoing conversions are represented schematically as follows:



wherein  $q'$  is 0-4, and all other variables are defined according to any process described above.

The process of converting a compound of formula (I-K) to a compound of formula (I-N) is carried out by reacting a compound of formula (I-K) with an imine in the presence of a palladium (0) source, a base and a suitable ligand, followed by hydrolysis to give a compound of formula (I-N). See J. Wolfe, et al., *Tetrahedron Letters* 38:6367-6370 (1997). Typically the imine is benzophenoneimine, the palladium (0) source is tris(dibenzylideneacetone)dipalladium(0), the base is sodium *tert*-butoxide and the ligand is *racemic*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. Suitable solvents include *N,N*-dimethylformamide and the like.

Reaction of a compound of formula (I-N) with compound of formula  $R^7$ -halogen in a suitable solvent in the presence of base, optionally with heating may be used to prepare compounds of formula (I-O). Typically the base is triethylamine or pyridine and the solvent is *N,N*-dimethylformamide and the like. Other transformations well

known to those skilled in the art for use with anilines may be used to convert a compound of formula (I-N) to a compound of formula (I-O).

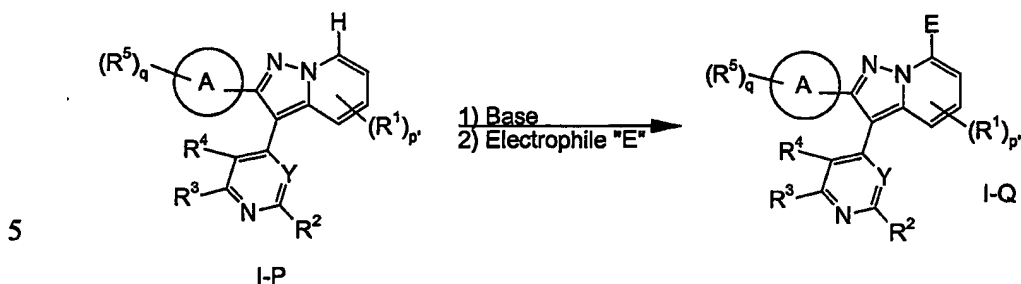
Additional compounds of formula (I-O) can be obtained by reductive amination of  
5 compounds of formula (I-N) with ketones or aldehydes. See, A. Abdel-Magid, et al., *J. Org. Chem.* 61:3849-3862 (1996). Typically a compound of formula (I-N) is treated with an aldehyde or a ketone in the presence of an acid, such as acetic acid, and a reducing agent, such as sodium triacetoxyborohydride and the like, in an inert solvent such as dichloroethane and the like.

10

The foregoing reaction methods can also be used to convert a compound of formula (I) wherein at least one  $R^1$  is halo to a compound of formula (I) wherein at least one  $R^1$  is  $-NH_2$ . In another embodiment, the foregoing methods are employed to make the same conversion when  $R^3$  or  $R^4$  is halo, to prepare a compound of formula (I) wherein  
15  $R^3$  or  $R^4$  is  $-NH_2$  or a compound of formula (I) wherein  $R^3$  or  $R^4$  is  $-NR^7R^8$  (where  $R^7$  and  $R^8$  are not both H).

As previously described, another method for converting a compound of formula (I-K) directly to a compound of formula (I-O) involves heating a compound of formula (I-K)  
20 with a amine to thermally displace the halogen.

In the embodiment where a compound of formula (I) is defined where  $R^1$  is not located at C-7, the compound of formula (I-P) may be converted to a compound of formula (I-Q). For example, a compound of formula (I-P) may be converted to a  
25 compound of formula (I-Q) by a deprotonation/electrophile quench protocol. For example, reaction of a compound of formula (I-P) with a base, such as n-butyllithium, followed by reacting with an electrophilic agent gives compounds of formula (I-Q).



wherein  $p'$  is 0-2 and E is selected from halo, alkyl,  $R^{10}$ cycloalkyl,  $-C(O)R^9$ ,  $-C(O)Ay$ ,  $-C(O)Het$ ,  $-CO_2R^8$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ay$  and  $-S(O)_nR^9$ , and all other variables are as defined in connection with any processes described above.

10

Electrophiles which may be used in this process include, but are not limited to: halogens (E=iodo, bromo, chloro), alkyl halides (E = methyl, benzyl etc.); aldehydes (E =  $CH(OH)R^{10}$ ); dimethylformamide (E = CHO); dialkyl disulfide (E = SMe, SEt, S-isopropyl etc); carbon dioxide (E =  $CO_2H$ ); dimethylcarbamoyl chloride (E =  $C(O)NMe_2$ ) and the like.

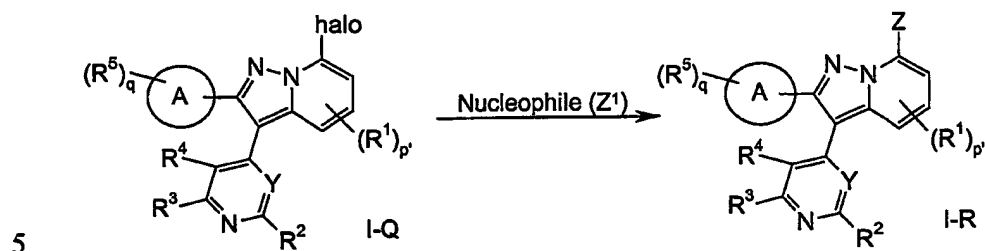
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Typically a compound of formula (I-P) in an inert solvent such as tetrahydrofuran at  $-78^\circ C$  is treated with a nonnucleophilic base. This reaction is subsequently quenched by addition of an electrophile. Suitable nonnucleophilic bases include, but are not limited to, n-butyllithium, lithium diisopropylamide, lithium tetramethylpiperidide and the like.

20

Further, compounds of formula (I) wherein  $R^1$  is not located at C-7, may be converted to other compounds of formula (I), by a deprotonation/electrophile quench/nucleophilic displacement protocol. For example, reaction of a compound of formula (I-P) with a base, such as n-butyllithium, followed by quenching with an electrophilic halogenating agent gives a compound of formula (I-Q) where E is halogen, as outlined in the previous scheme. Treatment of compound of formula (I-Q), where E is halogen with a nucleophile ( $Z'$ ) in a suitable solvent optionally with heating and optionally in the presence of a base gives a compound of formula (I-R).

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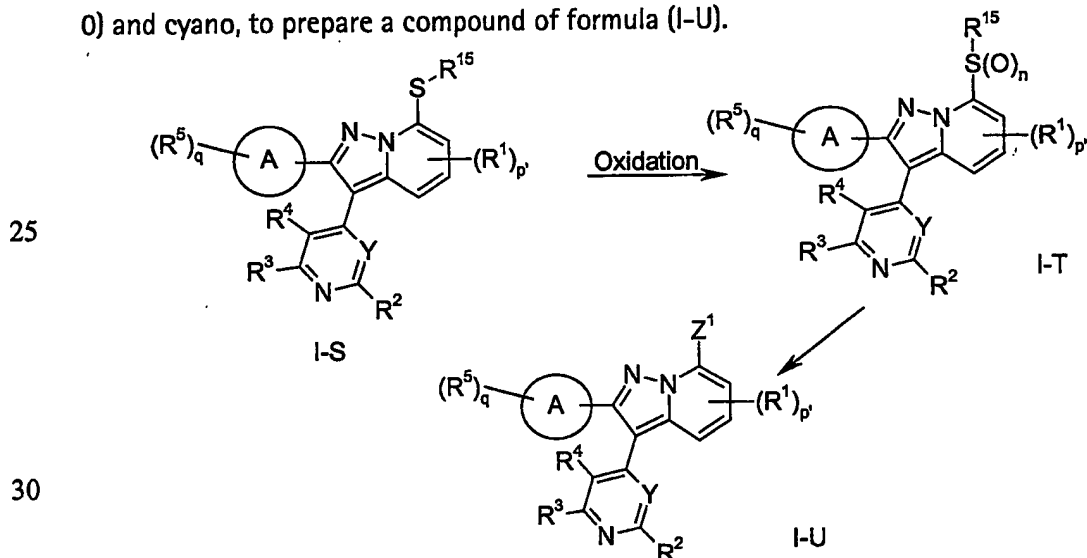


wherein  $p'$  is 0-3,  $Z^1$  is selected from the group consisting of  $-NHR^{10}Ay$ ,  $-NR^7Ay$ , Het,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-OR^7$ ,  $-OAy$ ,  $-OR^{10}Ay$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-NR^7R^8$ ,  $-S(O)_nR^9$  (where  $n$  is 0), cyano and all other variables are as defined according to any process described above.

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Solvents for use in this reaction include but are not limited to tetrahydrofuran, diethylether, and 1-methyl-2-pyrrolidinone. The base may be sodium hydride, sodium-tert-butoxide, potassium carbonate or the like.

15 As another example, one method of converting a compound of formula (I) to another compound of formula (I) comprises a) oxidizing the compound of formula (I-S), where  $R^1$  is  $-SR^{15}$  and  $R^{15}$  is alkyl, cycloalkyl or  $Ay$  and is located at C-7, to prepare a compound of formula (I-T) and then b) optionally reacting a compound of formula (I-T) with a nucleophile  $Z^1$  selected from the group consisting of  $-NHR^{10}Ay$ ,  $-NR^7Ay$ , Het,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-OR^7$ ,  $-OAy$ ,  $-OR^{10}Ay$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-NR^7R^8$ ,  $-S(O)_nR^9$  (where  $n$  is 0) and cyano, to prepare a compound of formula (I-U).



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wherein  $p'$  is 0-3;  $Z^1$  is selected from the group consisting of  $-NHR^{10}Ay$ ,  $-NR^7Ay$ , Het,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-OR^7$ ,  $-OAy$ ,  $-OR^{10}Ay$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-NR^7R^8$ ,  $-S(O)_nR^9$  (where  $n$  is 0) and cyano;  $R^{15}$  is alkyl, cycloalkyl or  $Ay$ ; and all other variables are as defined according to any processes described above.

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Based upon this disclosure and the examples contained herein one skilled in the art can readily convert a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof into another compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

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The present invention also provides radiolabeled compounds of formula (I) and biotinylated compounds of formula (I). Radiolabeled compounds of formula (I) and biotinylated compounds of formula (I) can be prepared using conventional techniques.

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For example, radiolabeled compounds of formula (I) can be prepared by reacting the compound of formula (I) with tritium gas in the presence of an appropriate catalyst to produce radiolabeled compounds of formula (I). In one preferred embodiment, the compounds of formula (I) are tritiated.

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The radiolabeled compounds of formula (I) and the biotinylated compounds of formula (I) are useful in assays for the identification of compounds for the treatment or prophylaxis of viral infections such as herpes viral infections. Accordingly, the present invention provides an assay method for identifying compounds which have activity for the treatment or prophylaxis of viral infections such as herpes viral

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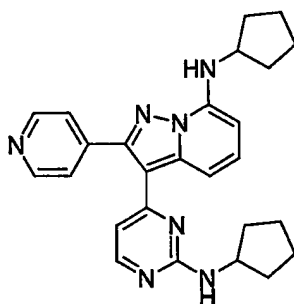
infections, which method comprises the step of specifically binding the radiolabeled compound of formula (I) or the biotinylated compounds of formula (I) to the target protein. More specifically, suitable assay methods will include competition binding assays. The radiolabeled compounds of formula (I) can be employed in assays according to the methods conventional in the art.

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The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way, the invention being defined by the claims which

follow. Reagents are commercially available or are prepared according to procedures in the literature. Example numbers refer to those compounds listed in the tables above.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained on Varian Unity Plus NMR spectrophotometers at 300 or 400 MHz, and 75 or 100 MHz respectively.  $^{19}\text{F}$  NMR were recorded at 282 MHz. Mass spectra were obtained on Micromass Platform, or ZMD mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). Analytical thin layer chromatography was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterization, and to follow the progress of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230–400 mesh), and the stated solvent system under pressure. All compounds were characterized as their free-base form unless otherwise stated. On occasion the corresponding hydrochloride salts were formed to generate solids where noted.

Example 1: *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine.



a) 2-(6-Chloro-2-pyridinyl)-1-(4-pyridinyl)ethanone oxime.

To a cold (0 °C) solution of 6-chloro-2-picoline (14.5 mL, 132.3 mmol) and ethyl isonicotinate (20.0 g, 132.3 mmol) in tetrahydrofuran (300 mL) was added lithium bis(trimethylsilyl)amide (280 mL, 1.0 M in tetrahydrofuran, 278 mmol) dropwise *via* a pressure equalizing funnel over 1 hour. Upon complete addition, the cold bath was removed and the resulting solution was heated at 45 °C for 15 hours. The mixture was cooled to room temperature, methanol was added, and the solution was concentrated

to give 2-(6-chloro-2-pyridinyl)-1-(4-pyridinyl)ethanone as a syrup, that was used without further purification. This syrup (11.7 g, 50 mmol) was dissolved in methanol (200 mL). To this solution was added hydroxylamine hydrochloride (17.5 g, 250 mmol) followed by the addition of a sodium hydroxide solution (10 g, 250 mmol in 30 mL of water). The resulting suspension was heated at reflux for 2 hours and then allowed to cool to room temperature. The mixture was concentrated and water was added to the resulting slurry. A white precipitate formed, which was collected by filtration, washed with water and dried to give 2-(6-chloro-2-pyridinyl)-1-(4-pyridinyl)ethanone oxime (10.5 g, 85%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.6 (broad s, 1H), 8.65 (d, 2H), 7.70 (d, 2H), 7.58 (t, 1H), 7.22 (m, 2H), 4.40 (s, 2H); MS *m/z* 248 (M+1).

b) 7-Chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridine.

To a solution of 2-(6-chloro-2-pyridinyl)-1-(4-pyridinyl)ethanone oxime (6.0 g, 24 mmol) in 1,2-dimethoxyethane (40 mL) at 0 °C was added trifluoroacetic anhydride (3.4 mL, 24 mmol), keeping the temperature below 10 °C during the addition. After the addition was complete, the reaction was warmed to room temperature. The solution was then cooled to 4 °C and a solution of triethylamine (6.7 mL, 48 mmol) in 1,2-dimethoxyethane (15 mL) was added over a period of 0.5 hours. The mixture was allowed to warm to room temperature and was stirred for 1.5 hours. To this mixture was added iron(II) chloride (50 mg) and the reaction was heated at 75 °C for 15 hours. The reaction mixture was poured into water (300 mL). The resulting suspension was extracted with ethyl acetate. The ethyl acetate phase was dried (magnesium sulfate), filtered and concentrated to a solid residue. This residue was purified by silica gel chromatography (1:1 ethyl acetate-hexane) to give 7-chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridine (2.8 g, 50%) as a tan solid. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO): δ 8.62 (m, 2H), 7.93 (m, 2H), 7.76 (dd, 1H), 7.42 (m, 2H), 7.24 (m, 1H); MS *m/z* 230 (M+1).

c) 1-[7-Chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone.

To a solution of 7-chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridine (2.0 g, 8.7 mmol) in acetonitrile (50 mL) at room temperature was added acetic anhydride (2.0 mL, 21

mmol). Boron trifluoride diethyletherate (5.3 mL, 42 mmol) was added dropwise and the resulting solution was heated at 80 °C for 12 hours. The reaction mixture was cooled to room temperature and quenched by the dropwise addition of saturated sodium bicarbonate. The reaction mixture was extracted with ethyl acetate, and the organic phase washed with brine, dried (magnesium sulfate), filtered and concentrated. The residue was purified by silica gel chromatography (5:95 methanol-dichloromethane) to give 1-[7-chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (1.53 g, 65%) as a red foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.82 (m, 2H), 8.45 (d, 1H), 7.62 (m, 2H), 7.54 (t, 1H), 7.25 (d, 1H), 2.26 (s, 3H); MS *m/z* 272 (M+1).

d) 1-[7-(Cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone.

To a solution of 1-[7-chloro-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.68 g, 2.5 mmol) in toluene (10 mL) was added successively *rac*-2,2'-

bis(diphenylphosphino)-1,1'-binaphthyl (100 mg, 0.15 mmol), cesium carbonate (1.2 g,

3.8 mmol), cyclopentylamine (1.5 mL, 12.5 mmol), and palladium (II) acetate (25 mg, 0.1 mmol). The resulting mixture was stirred at 90 °C for 24 hours, at which time the reaction was judged complete by thin layer chromatography. The solution was cooled to room temperature and ethyl acetate and water were added to the reaction mixture.

The phases were separated, and the aqueous phase again extracted with ethyl acetate. The combined organic phases were dried (magnesium sulfate), filtered and concentrated. The resulting residue was purified by flash chromatography (1:1 hexanes-ethyl acetate) to give 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.64 g, 80%) as a yellow foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.80 (d, 2H), 7.65 (d, 1H), 7.60 (d, 2H), 7.50 (t, 1H), 6.20 (d, 1H), 6.06 (d, 1H), 4.0 (m, 1H), 2.26 (s, 3H), 1.6-2.2 (m, 8H); MS *m/z* 321 (M+1).

e) *N*-Cyclopentylguanidine hydrochloride.

This compound was prepared by modification of a procedure from Bannard, R. A. B.; Casselman, A. A.; Cockburn, W.F.; and Brown, G. M. *Can. J. Chem.* 1958, 36, 1541-

1549). To a solution of 2-methyl-2-thiopseudourea sulfate (13.9 g, 50.0 mmol) in water (40 mL) was added cyclopentylamine (14.8 mL, 150 mmol). The resultant mixture was heated to 55 °C for 20 minutes and then to reflux for 2.5 hours. The

mixture was cooled to room temperature and concentrated *in vacuo* and azeotroped with methanol. Water was added (~100 mL) and Amberlite IRA 400 (Cl<sup>-</sup>) resin was added. The mixture was stirred for 1 hour and then the resin was removed by filtration. The solution was concentrated *in vacuo* and azeotroped with methanol.

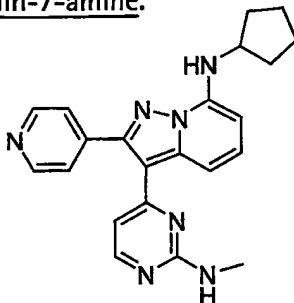
- 5 The residue was recrystallized from methanol-acetone to yield *N*-cyclopentylguanidine hydrochloride (7.0 g, 86%) as a fine white solid. <sup>1</sup>H NMR (D<sub>2</sub>O): δ 3.62 (m, 1 H), 1.75 (m, 2 H), 1.52-1.32 (m, 6 H); <sup>13</sup>C NMR (D<sub>2</sub>O) δ 156.23, 53.11, 32.15, 23.13; MS *m/z* 128 (M+1).

- 10 f) *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine.

A solution of 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.3 g, 0.94 mmol) in *N,N*-dimethylformamide dimethyl acetal (10 mL) was heated at reflux for 3 days. The mixture was allowed to cool to room temperature.

- 15 Water was added and the resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was dried (magnesium sulfate), filtered and concentrated. The resulting residue was purified by flash chromatography (7:3 ethyl acetate-acetone) to give 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (0.23 g, 65%) as a colored syrup which was used in
- 20 the next step without further purification. To a solution of 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (0.10 g, 0.27 mmol) in tetrahydrofuran (10 mL) was added cyclopentyl guanidine hydrochloride (0.06 g, 0.38 mmol) followed by potassium *tert*-butoxide (0.085 g, 0.76 mmol). The resulting mixture was heated at reflux for 12 hours. Upon cooling to room
- 25 temperature, water was added. The mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:9 methanol-dichloromethane) to give the title compound (89 mg, 75%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.64 (d, 2H), 8.04 (d, 1H), 7.58 (m, 3H), 7.28 (t, 1H), 6.32 (d, 1H), 6.02 (d, 1H), 5.95 (d, 1H), 5.03 (d, 1H), 4.22 (m, 1H), 3.97 (m, 1H), 1.2-2.2 (m, 16H);
- 30 MS *m/z* 440 (M+1).

Example 2: N-Cyclopentyl-3-[2-(methylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine.

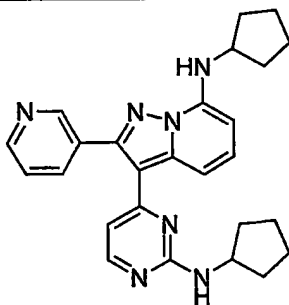


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To a solution of 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (From example 1, 0.13 g, 0.35 mmol) in tetrahydrofuran (10 mL) was added cyclopentyl guanidine hydrochloride (0.06 g, 0.38 mmol) followed by potassium *tert*-butoxide (0.085 g, 0.76 mmol). The resulting mixture was heated at reflux for 12 hours. Upon cooling to room temperature, water was added. The mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:20 methanol-ethyl acetate) to give the title compound (100 mg, 75%) as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.72 (d, 2H), 8.13 (d, 1H), 7.65 (m, 3H), 7.35 (t, 1H), 6.43 (d, 1H), 6.10 (d, 1H), 6.05 (d, 1H), 5.10 (m, 1H), 4.05 (m, 1H), 3.05 (d, 3H), 1.2-2.2 (m, 8H); MS *m/z* 386 (M+1).

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Example 3: N-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine.



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a) 2-(6-Chloro-2-pyridinyl)-1-(3-pyridinyl)ethanone oxime.

In a similar manner as described in Example 1 from 6-chloro-2-picoline (9.3 g, 73 mmol) and methyl nicotinate (10.0 g, 73 mmol), 2-(6-chloro-2-pyridinyl)-1-(3-pyridinyl)ethanone was obtained as a syrup. This syrup (10 g, 70 mmol) was treated with hydroxylamine hydrochloride (24.3 g, 350 mmol) followed by the addition of a sodium hydroxide solution (14 g, 350 mmol in 30 mL of water) as described in example 1 to give 2-(6-chloro-2-pyridinyl)-1-(3-pyridinyl)ethanone oxime (14.4 g, 80%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.84 (d, 1H), 8.40 (dd, 1H), 8.00 (m, 1H), 7.50 (t, 1H), 7.2-7.4 (m, 3H), 4.26 (s, 2H); MS *m/z* 248 (M+1).

b) 7-Chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridine.

In a similar manner as described in Example 1 from 2-(6-chloro-2-pyridinyl)-1-(3-pyridinyl)ethanone oxime (9.6 g, 39 mmol) was obtained 7-chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridine (2.8 g, 50%) as a tan solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.20 (d, 1H), 8.64 (dd, 1H), 8.44 (dt, 1H), 7.56 (d, 1H), 7.48 (dd, 1H), 7.14 (dd, 1H), 7.0 (s, 1H), 6.96 (d, 1H); MS *m/z* 230 (M+1).

c) 1-[7-Chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone.

In a similar manner as described in Example 1 from 7-chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridine (1.5 g, 6.5 mmol) was obtained 1-[7-chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (1.4 g, 60%) as a foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.90 (broad s, 1H), 8.77 (d, 1H), 8.40 (d, 1H), 8.00 (dt, 1H), 7.50 (m, 2H), 7.20 (d, 1H), 2.21 (s, 3H); MS *m/z* 272 (M+1).

d) 1-[7-(Cyclopentylamino)-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone.

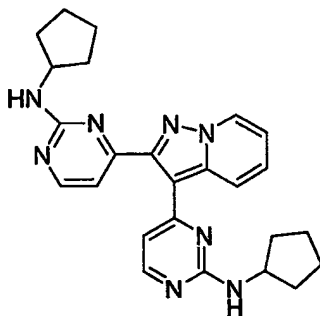
In a similar manner as described in Example 1 from 1-[7-chloro-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.95 g, 3.5 mmol) was obtained 1-[7-(cyclopentylamino)-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.78 g, 70%) as a yellow foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.88 (s, 1H), 8.73 (m, 1H), 8.01 (d, 1H), 7.61 (d, 1H), 7.44 (m, 2H), 6.17 (d, 1H), 6.05 (d, 1H), 4.00 (m, 1H), 2.23 (s, 3H), 1.6-2.2 (m, 8H); MS *m/z* 321 (M+1).

e) *N*-Cyclopentyl-3-[2-(cyclopentylmethyl)-4-pyrimidinyl]-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine.

In a similar manner as described in Example 1 from 1-[7-(cyclopentylamino)-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (0.56 g, 1.8 mmol) was obtained *N*-

cyclopentyl-3-[2-(cyclopentylmethyl)-4-pyrimidinyl]-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine (192 mg, 25% over 2 steps) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.90 (s, 1H), 8.63 (m, 1H), 8.05 (d, 1H), 7.95 (m, 1H), 7.65 (d, 1H), 7.3 (m, 2H), 6.30 (d, 1H), 6.0 (m, 1H), 5.35 (d, 1H), 4.25 (m, 2H), 3.98 (m, 1H), 1.5-2.2 (m, 16H); MS *m/z* 440 (M+1).

Example 4: *N*-Cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)amine.



a) 4-Ethynyl-2-(methylsulfanyl)pyrimidine.

4-Iodo-2-(methylsulfanyl)pyrimidine (2.0 g, 8.1 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). To this solution was added triethylamine (1.4 mL, 10.1 mmol), copper (I) iodide (80 mg, 0.4 mmol) and dichlorobis(triphenylphosphine) palladium (II) (140 mg, 0.24 mmol). (Trimethylsilyl)acetylene (1.4 mL, 10.1 mmol) was added

dropwise to the resulting solution. After the addition of (trimethylsilyl)acetylene was complete the reaction was stirred at room temperature for 2 hours. Hexane was added to the reaction mixture and the mixture was filtered to remove precipitates. The solution was concentrated to give a syrup, that was purified by silica gel chromatography (1:1 ethyl acetate:hexane) to give 1.76 g (99 %) of 2-

(methylsulfanyl)-4-[(trimethylsilyl)ethynyl]pyrimidine. 2-(Methylsulfanyl)-4-[(trimethylsilyl)ethynyl]pyrimidine (1.76 g, 8.0 mmol) was dissolved in methanol (60

mL). To this solution was added potassium fluoride (467 mg, 8.0 mmol) and the resulting mixture stirred at room temperature for 5 minutes. The solution was concentrated and ethyl acetate and water were added. The phases were separated and the aqueous phase extracted with additional ethyl acetate. The organics were  
5 combined, dried over magnesium sulfate, filtered and concentrated to give 1.0 g (83 %) of 4-ethynyl-2-(methylsulfanyl)pyrimidine as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.51 (d, 1H), 7.06 (d, 1H), 3.34 (s, 1H), 2.56 (s, 3H); MS *m/z* 151 (M+1).

b) 2-(Methylsulfanyl)-4-{[2-(methylsulfanyl)-4-pyrimidinyl]ethynyl}pyrimidine.  
10 4-Iodo-2-(methylsulfanyl)pyrimidine (1.76 g, 7.1 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). To this solution was added triethylamine (1.2 mL, 8.5 mmol), copper (I) iodide (70 mg, 0.4 mmol) and dichlorobis(triphenylphosphine)palladium (II) (150 mg, 0.21 mmol). A solution of 4-ethynyl-2-(methylsulfanyl)pyrimidine (1.0 g, 7.1 mmol) in tetrahydrofuran was added dropwise. The reaction mixture was stirred at  
15 room temperature overnight. Ethyl acetate and water were added to the reaction mixture. The phases were separated and the aqueous phase extracted with additional ethyl acetate. The organics were combined, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (1:1 ethyl acetate:hexane) gave 1.35 g (69 %) of 2-(methylsulfanyl)-4-{[2-(methylsulfanyl)-4-  
20 pyrimidinyl]ethynyl}pyrimidine as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.57 (d, 2H), 7.19 (d, 2H), 2.59 (s, 6H); MS *m/z* 275 (M+1).

c) 2,3-Bis[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine.  
2-(Methylsulfanyl)-4-{[2-(methylsulfanyl)-4-pyrimidinyl]ethynyl}pyrimidine (0.1 g,  
25 0.37 mmol) was dissolved in acetonitrile (5 mL). To this solution was added 1-aminopyridinium iodide (81 mg, 0.37 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.056 mL, 0.37 mmol) and the resulting mixture was stirred at room temperature overnight. The resulting reddish suspension was concentrated *in vacuo*. Ethyl acetate and water were added to this residue. The phases were separated and the aqueous  
30 phase extracted with additional ethyl acetate. The organics were combined, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel

chromatography (1:1 ethyl acetate:hexane) gave 95 mg (71 %) of 2,3-bis[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.64 (d, 1H), 8.53 (d, 1H), 8.41 (d, 1H), 8.31 (d, 1H), 7.56 (d, 1H), 7.37 (t, 1H), 7.13 (d, 1H), 7.00 (t, 1H), 2.59 (s, 3H), 2.37 (s, 3H); MS *m/z* 367 (M+1).

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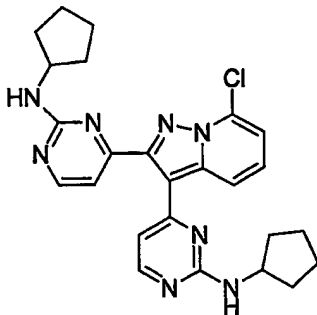
d) *N*-Cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)amine.

2,3-Bis[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (0.35 g, 0.96 mmol) was dissolved in dichloromethane (20 mL) and the resulting solution cooled to 0°C in an ice bath. To this solution was added dropwise 3-chloroperoxybenzoic acid (824 mg, 57-86 %) in dichloromethane. This reaction mixture was stirred at 0°C for 10 minutes. Additional dichloromethane was added and the reaction mixture was extracted with saturated aqueous potassium carbonate. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a foam. This foam was dissolved in cyclopentylamine and heated to 60 °C for 2 hours. The resulting mixture was concentrated to a solid that was recrystallized from acetonitrile to give 210 mg (50 %) of *N*-cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)amine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.52 (d, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.29 (t, 1H), 6.90 (m, 2H), 6.62 (d, 1H), 5.23 (m, 2H), 4.30 (m, 1H), 4.20 (broad s, 1H), 1.8-2.1 (m, 4H), 1.4-1.8 (m, 12H); MS *m/z* 441 (M+1).

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Example 5: *N*-(4-{7-Chloro-2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)-*N*-cyclopentylamine.

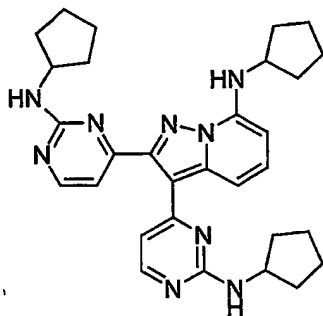
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*N*-Cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)amine (140 mg, 0.32 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL). The resulting solution was cooled to -78 °C, then *n*-butyllithium (0.99 mL, 1.6 mmol, 1.6 M in hexane) was added dropwise. The resulting dark solution was stirred at -78 °C for 20 minutes, then carbon tetrachloride (2 mL) was added. The reaction was stirred for additional 20 minutes and then quenched by the addition of water and allowed to warm to room temperature. The phases were separated and the aqueous phase extracted with ethyl acetate. The organics were combined, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (1:1 ethyl acetate:hexane) gave 80 mg (53 %) of *N*-(4-{7-chloro-2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)-*N*-cyclopentylamine as a foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.37 (d, 1H), 8.27 (d, 1H), 8.16 (d, 1H), 7.26 (t, 1H), 7.06 (d, 1H), 7.04 (m, 1H), 6.62 (d, 1H), 5.21 (d, 1H), 5.15 (d, 1H), 4.32 (m, 1H), 4.10 (m, 1H), 1.4-2.1 (m, 16H); MS *m/z* 475 (M+1).

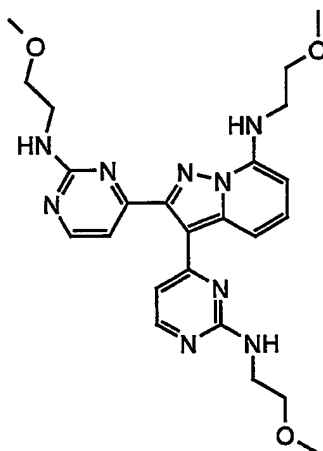
Example 6: *N*-Cyclopentyl-2,3-bis[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine.



a) *N*-(4-{7-Chloro-2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)-*N*-cyclopentylamine (60 mg, 0.13 mmol) was dissolved in cyclopentylamine (4 mL). To this solution was added successively *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (31 mg, 0.05 mmol), cesium carbonate (61 mg, 0.18 mmol) and palladium (II) acetate (6 mg, 0.03 mmol). The resulting mixture was stirred at 90 °C for 24 hours, at which time the reaction was judged complete by thin layer chromatography. The solution was cooled to room temperature and ethyl acetate and water were added to the reaction mixture. The phases were separated,

and the aqueous phase again extracted with ethyl acetate. The combined organic phases were dried (magnesium sulfate), filtered and concentrated. The resulting residue was purified by flash chromatography (1:1 hexanes:ethyl acetate) to give 20 mg (30 %) of *N*-cyclopentyl-2,3-bis[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-  
5 *a*]pyridin-7-amine as a foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.38 (d, 1H), 8.02 (broad s, 1H), 7.63 (d, 1H), 7.33 (t, 1H), 6.93 (s, 1H), 6.59 (d, 1H), 6.07 (d, 1H), 6.03 (m, 1H), 5.21 (m, 1H), 4.32 (m, 1H), 4.23 (m, 1H), 4.00 (m, 1H), 1.4-2.2 (m, 24H); MS *m/z* 524 (M+1).

Example 7: N-(2-Methoxyethyl)-2,3-bis{2-[(2-methoxyethyl)amino]pyrimidin-4-  
10 yl}pyrazolo[1,5-*a*]pyridin-7-amine



To a -78°C solution of 2,3-bis[2-(methylsulfany)pyrimidin-4-yl]pyrazolo[1,5-  
*a*]pyridine (0.72 g, 2.0 mmol) in tetrahydrofuran (50 mL) was added a 2 M solution of  
25 lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (2.9 mL, 5.9mmol)  
dropwise. The reaction mixture was stirred for 15 minutes, then carbon tetrachloride  
(5 mL) was added. The reaction mixture was stirred for 1 hour and quenched with  
brine and extracted with ethyl acetate (3x25 mL). The organic phase was washed with  
brine (3x25 mL), dried over magnesium sulfate, and concentrated under reduced  
30 pressure. The residue was purified by silica gel chromatography (1:9  
acetone:dichloromethane) to give 260 mg (32 %) of 7-chloro-2,3-bis[2-  
(methylsulfany)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine. 7-Chloro-2,3-bis[2-  
(methylsulfany)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine (0.098 g, 0.24 mmol) was  
dissolved in dichloromethane (3 mL) and cooled to 0 °C. To the solution was added 3-

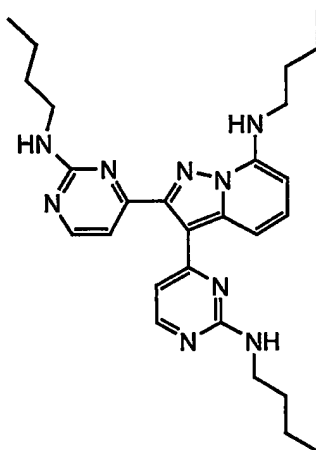
chloroperoxybenzoic acid (0.13 g, 0.73 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, and concentrated under reduced pressure. To 7-chloro-2,3-bis[2-

5 (methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine (0.027 g, 0.062 mmol) was added 2-methoxyethylamine (2 mL) and the reaction was heated to 100 °C in a sealed tube overnight. The reaction mixture was cooled to room temperature and concentrated by evaporation under reduced pressure. The residue was purified by silica gel chromatography eluting with 1 : 1 acetone : dichloromethane to give 15 mg  
10 (49 %) of *N*-(2-methoxyethyl)-2,3-bis{2-[(2-methoxyethyl)amino]pyrimidin-4-yl}pyrazolo[1,5-*a*]pyridin-7-amine. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.41 (d, 1H), 8.16 (d, 1H), 7.69 (d, 1H), 7.36 (d, 1H), 7.05 (m, 1H), 6.65 (d, 1H), 6.33 (t, 1H), 6.09 (d, 1H), 5.57 (m, 1H), 5.42 (t, 1H), 3.37-3.80 (m, 21H); MS *m/z* 494 (M+1).

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Example 8: *N*-Butyl-2,3-bis[2-(butylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine.

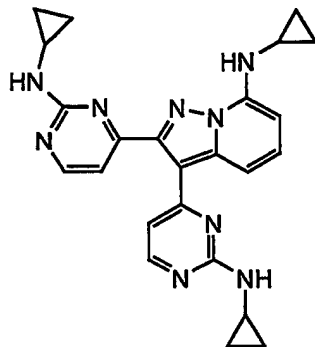
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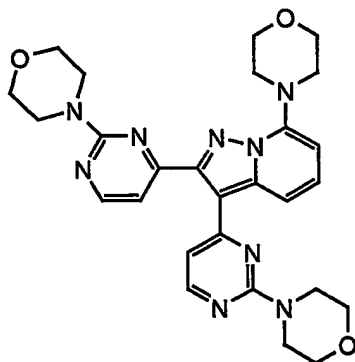
*N*-Butyl-2,3-bis[2-(butylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine was prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine with *n*-butylamine as described in Example 7. <sup>1</sup>H NMR, (400 MHz, CDCl<sub>3</sub>): δ  
30 8.35 (d, 1H), 8.09 (d, 1H), 7.62 (d, 1H), 7.30 (t, 1H), 6.93 (m, 1H), 6.57 (d, 1H), 6.40 (d, 1H), 6.20 (d, 1H), 5.17 (m, 1H), 5.08 (m, 1H), 3.34-3.46 (m, 6H), 1.75 (m, 2H), 1.35-1.66 (m, 10H), 0.90-1.00 (m, 9H); MS *m/z* 488 (M+1).

Example 9: *N*-Cyclopropyl-2,3-bis[2-(cyclopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine.



- 5
- 10 *N*-Cyclopropyl-2,3-bis[2-(cyclopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine was prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine with cyclopropylamine as described in Example 7. <sup>1</sup>H NMR, (CDCl<sub>3</sub>): δ 8.47 (d, 1H), 8.19 (d, 1H), 7.86 (d, 1H), 7.37 (t, 1H), 7.04 (d, 1H), 6.71 (d, 1H), 6.44 (d, 1H), 6.36 (s, 1H), 5.53 (s, 1H), 5.39 (s, 1H), 2.62-2.90 (m, 3H), 0.77-0.96 (m, 8H),
- 15 0.56-0.70 (m, 4H); MS *m/z* 440 (M+1).

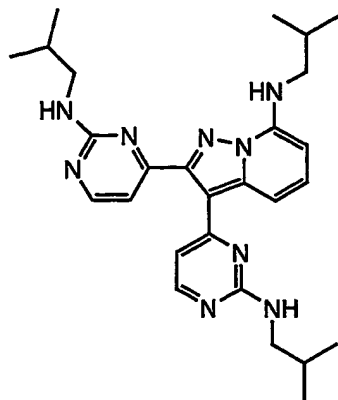
Example 10: 7-Morpholin-4-yl-2,3-bis[2-morpholin-4-ylpyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine.



- 20
- 25 7-Morpholin-4-yl-2,3-bis[2-morpholin-4-ylpyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine was prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine with morpholine as described in Example 7. <sup>1</sup>H NMR, (400 MHz, CDCl<sub>3</sub>): δ 8.43 (d, 1H), 8.21 (d, 1H), 7.83 (d, 1H), 7.28 (dd, 1H), 7.19 (d, 1H), 6.71 (d, 1H), 6.34 (d, 1H), 4.01 (t, 4H), 3.80 (m, 8H), 3.67 (m, 8H), 3.49 (m, 4H); MS *m/z* 530 (M+1).
- 30

Example 11: *N*-Isobutyl-2,3-bis[2-(isobutylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine.

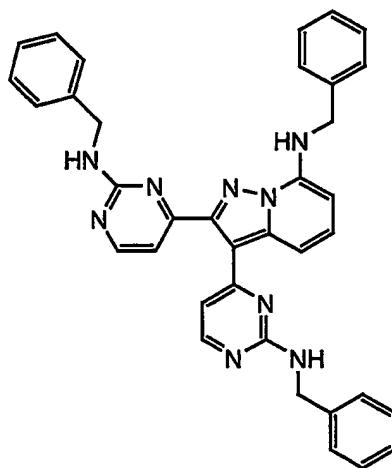
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- 10 *N*-Isobutyl-2,3-bis[2-(isobutylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine  
pyridine was prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-  
yl]pyrazolo[1,5-*a*]pyridine with isobutylamine as described in Example 7. <sup>1</sup>H NMR,  
(400 MHz, CDCl<sub>3</sub>): δ 8.35 (d, 1H), 8.09 (d, 1H), 7.59 (d, 1H), 7.30 (d, 1H), 6.94 (bs, 1H),  
6.57 (m, 1H), 6.16 (t, 1H), 6.00 (d, 1H), 5.26 (bs, 1H), 5.17 (bs, 1H), 3.25 (t, 3H), 3.18 (t,  
15 3H), 2.00-2.15 (m, 1H), 1.85-1.95 (m, 2H), 0.90-1.10 (m, 18H); MS *m/z* 488 (M+1).

Example 12: *N*-Benzyl-2,3-bis[2-(benzylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine.

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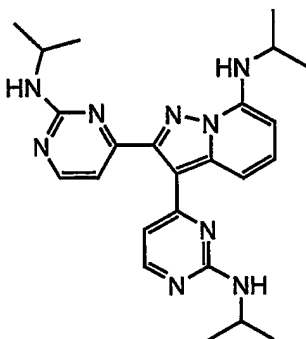


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- N*-Benzyl-2,3-bis[2-(benzylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine was  
prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-  
30 *a*]pyridine with benzylamine as described in Example 7. <sup>1</sup>H NMR, (400 MHz, CDCl<sub>3</sub>): δ  
8.37 (d, 1H), 8.02 (d, 1H), 7.16-7.40 (m, 16H), 7.12 (t, 1H), 7.02 (bs, 1H), 6.63 (d, 1H),

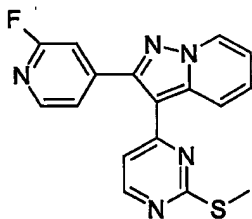
6.48 (t, 1H), 5.96 (d, 1H), 5.58 (bs, 1H), 5.46 (1H), 4.65 (d, 2H), 4.38-4.62 (m, 4H); MS  $m/z$  590 (M+1).

Example 13: *N*-Isopropyl-2,3-bis[2-(isopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine.



*N*-Isopropyl-2,3-bis[2-(isopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine was prepared by treating 7-chloro-2,3-bis[2-(methylsulfinyl)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridine with isopropylamine as described in Example 7.  $^1\text{H}$  NMR, (CDCl<sub>3</sub>):  $\delta$  8.39 (d, 1H), 8.14 (d, 1H), 7.52 (m, 1H), 7.36 (d, 1H), 6.96 (m, 1H), 6.60 (d, 1H), 6.06 (d, 1H), 5.99 (d, 1H), 5.08 (m, 1H), 4.99 (m, 1H), 4.05-4.25 (m, 2H), 3.80-3.99 (m, 1H), 1.42 (d, 6H), 1.30 (d, 6H), 1.24 (m, 6H); MS  $m/z$  446 (M+1).

Example 14: 2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfonyl)-4-pyrimidinyl]pyrazolo-[1,5-*a*]pyridine.

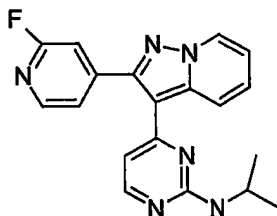


a) 4-[(2-Fluoro-4-pyridinyl)ethynyl]-2-(methylsulfonyl)pyrimidine.

4-Iodo-2-fluoropyridine (1.09 g, 4.9 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). To this solution was added triethylamine (0.9 mL, 6.5 mmol), copper (I) iodide (80 mg, 0.4 mmol) and dichlorobis(triphenylphosphine) palladium (II) (60 mg, 0.32 mmol). 4-Ethynyl-2-(methylsulfonyl)pyrimidine (example 4, 0.75 g, 4.9

- mmol) in tetrahydrofuran was added dropwise to the resulting solution. After the addition was complete the reaction was stirred at room temperature overnight. The mixture was concentrated to give a syrup, that was purified by silica gel chromatography (1:1 ethyl acetate:hexane) to give after removal of solvents 0.84 g (70 %) of 4-[(2-fluoro-4-pyridinyl)ethynyl]-2-(methylsulfanyl)pyrimidine as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.61 (d, 1H), 8.32 (d, 1H), 7.39 (d, 1H), 7.17 (m, 2H), 2.64 (s, 3H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -66.82; MS *m/z* 246 (M+1).
- b) 2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine. 4-[(2-Fluoro-4-pyridinyl)ethynyl]-2-(methylsulfanyl)pyrimidine (740 mg, 3.0 mmol) was dissolved in acetonitrile (10 mL). To this solution was added 1-aminopyridinium iodide (670 mg, 3.0 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.460 mL, 3.0 mmol) at 0 °C and the resulting mixture was allowed to warm to room temperature and stirred at room temperature for 2 days. The resulting reddish suspension was concentrated *in vacuo*. Ethyl acetate and water were added to this residue. The phases were separated and the aqueous phase extracted with additional ethyl acetate. The organics were combined, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (1:1 ethyl acetate:hexane) gave 550 mg (55 %) of 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.62 (d, 1H), 8.41 (d, 1H), 8.39 (d, 1H), 8.35 (d, 1H), 7.47 (m, 2H), 7.25 (m, 1H), 7.06 (dt, 1H), 6.83 (d, 1H), 2.53 (s, 3H); <sup>19</sup>F NMR δ (CDCl<sub>3</sub>): -67.12; <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 173.16, 164.23 (d, *J*<sub>CF</sub> 239.7 Hz), 159.67, 156.97, 150.17 (d, *J*<sub>CF</sub> 3.1 Hz), 148.29 (d, *J*<sub>CF</sub> 15.3 Hz), 146.73, (d, *J*<sub>CF</sub> 8.3 Hz), 141.07, 129.08, 127.10, 122.05 (d, *J*<sub>CF</sub> 3.8 Hz), 119.80, 114.82, 114.56, 110.07 (d, *J*<sub>CF</sub> 38.1 Hz), 107.96; MS 338 *m/z* (M+1).

Example 15: 4-[2-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine.

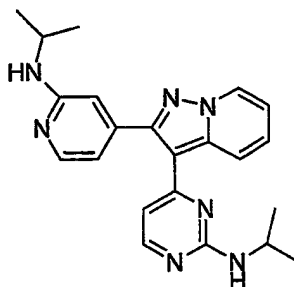


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2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (0.18 g, 0.53 mmol) was dissolved in dichloromethane (10 mL) and the resulting solution cooled to 0°C in an ice bath. To this solution was added dropwise 3-chloroperoxybenzoic acid (230 mg, 57-86 %) in dichloromethane. This reaction mixture was stirred at 0°C for 10 minutes. Additional dichloromethane was added and the reaction mixture was extracted with saturated aqueous potassium carbonate. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a foam. This foam was dissolved in isopropylamine and heated to 50 °C for 2 hours. The resulting mixture was concentrated to a solid that was purified by silica gel chromatography (1:1 ethyl acetate:hexane) give 90 mg (48 %) of the title compound as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.56 (d, 1H), 8.31 (m, 2H), 8.19 (d, 1H), 7.52 (m, 1H), 7.40 (t, 1H), 7.33 (broad s, 1H), 7.02 (t, 1H), 6.45 (d, 1H), 5.20 (m, 1H), 4.20 (m, 1H), 1.31 (d, 5H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -67.68; MS *m/z* 349 (M+1).

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Example 16: *N*-Isopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine.



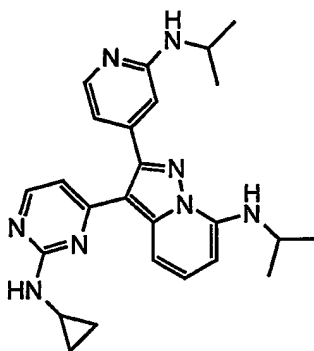
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4-[2-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine (80 mg, 0.23 mmol) was dissolved in isopropylamine (10 mL) in a pressure vessel and the resulting solution heated at 120 °C for 4 days. The resulting

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mixture was concentrated to a solid that was purified by silica gel chromatography (1:1 ethyl acetate:hexane) to give 50 mg (56 %) of the title compound as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.53 (d, 1H), 8.43 (d, 1H), 8.15 (two d, 2H), 7.35 (t, 1H), 6.96 (t, 1H), 6.82 (d, 1H), 6.65 (s, 1H), 6.50 (d, 1H), 5.08 (d, 1H), 4.60 (d, 1H), 4.25 (m, 1H), 3.94 (m, 1H), 1.33 (d, 6H), 1.25 (d, 6H); MS *m/z* 388 (M+1).

Example 17: 3-[2-(Cyclopropylamino)-4-pyrimidinyl]-N-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine.



a) 2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine.

To a cold (0 °C) solution of 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (1.81 g, 5.36 mmol) in dichloromethane (100 mL) was added 3-chloroperoxybenzoic acid (1.39 g, 70%, 5.63 mmol). The reaction mixture was warmed to room temperature and stirred 16 hours. The reaction mixture was diluted with 100 mL dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The organic layer was concentrated *in vacuo* to give 1.84 g of 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine of 90% purity as a greenish grey solid. This material was carried on without further purification. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.92 (d, 1H), 8.75 (d, 1H), 8.54 (d, 1H), 8.38 (d, 1H), 7.63-7.59 (m, 2H), 7.48 (s, 1H), 7.32 (d, 1H), 7.24 (t, 1H), 2.87 (s, 3H); <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>) δ -68.05; MS *m/z* 354 (M+1).

b) *N*-Cyclopropyl-4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine.

A solution of 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (430 mg, 90%, ~1.1 mmol) in cyclopropylamine (4 mL, 57.7 mmol) was heated at 45 °C in a sealed glass tube for 6 hours. The excess cyclopropylamine was removed *in vacuo* to provide crude *N*-cyclopropyl-4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (370 mg, 97%). A small portion of the crude material was chromatographed (19:1 dichloromethane:acetone to 9:1 dichloromethane:acetone) to provide material as a light yellow solid. R<sub>f</sub> 0.26 (9:1 dichloromethane:acetone); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.52 (d, 1H), 8.42 (d, 1H), 8.29 (d, 1H), 8.21 (d, 1H), 7.51 (d, 1H), 7.36 (d, 1H), 7.32 (s, 1H), 6.98 (t, 1H), 6.48 (d, 1H), 5.69 (br, 1H), 2.81 (m, 1H), 0.83 (m, 2H), 0.61 (m, 2H); MS *m/z* 347 (M+1).

c) *N*-Cyclopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine.

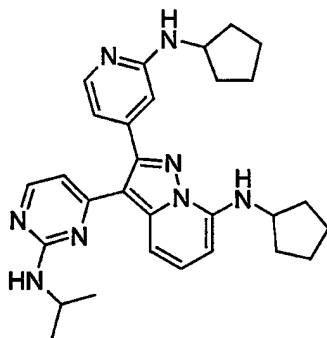
A solution of *N*-cyclopropyl-4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (206 mg, 0.595 mmol) in isopropylamine (3 mL, 35.2 mmol) was heated at 150 °C in a steel bomb for 16 hours. The excess isopropylamine was removed under a stream of nitrogen. The crude material was triturated with ether to provide *N*-cyclopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine (185 mg, 80%) as a tan solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.60 (d, 1H), 8.51 (d, 1H), 8.14 (m, 2H), 7.32 (t, 1H), 6.93 (t, 1H), 6.80 (d, 1H), 6.62 (s, 1H), 6.55 (d, 1H), 5.62 (br, 1H), 4.60 (d, 1H), 3.87 (m, 1H), 2.85 (m, 1H), 1.29 (d, 3H), 1.22 (d, 3H), 0.86 (m, 2H), 0.63 (m, 2H); MS *m/z* 386 (M+1).

d) 3-[2-(Cyclopropylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine.

To a cold (-78 °C) solution of *N*-cyclopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine (178 mg, 0.462 mmol) in tetrahydrofuran (15 mL) was added *n*-butyllithium (866 μL, 1.6 M in hexanes, 1.39

mmol) dropwise. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 30 minutes, then carbon tetrachloride (179  $\mu\text{L}$ , 1.85 mmol) was added dropwise. The resultant mixture was warmed to room temperature and stirred 2 hours. The reaction mixture was quenched with water and diluted with ethyl acetate. The organic layer was washed  
 5 with water and brine, then dried over magnesium sulfate. Filtration and concentration provided crude 4-{7-chloro-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-cyclopropyl-2-pyrimidinamine. This material was taken up in isopropylamine (3 mL, 35.2 mmol) and heated in a steel bomb at  $120^{\circ}\text{C}$  for 16 hours. The reaction mixture was cooled and the excess isopropylamine was  
 10 removed under a stream of nitrogen. Preparative HPLC provided 3-[2-(cyclopropylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine (10 mg, 5%) as a yellow solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.10-8.07 (m, 2H), 7.87 (d, 1H), 7.35 (t, 1H), 6.85 (d, 1H), 6.69 (s, 1H), 6.51 (d, 1H), 6.06 (d, 1H), 5.94 (d, 1H), 5.68 (br, 1H), 4.16 (br, 1H), 3.93-3.79 (m, 2H), 2.85 (m,  
 15 1H), 1.40 (d, 6H), 1.25 (d, 6H), 0.87 (m, 2H), 0.64 (m, 2H); MS  $m/z$  443 ( $M+1$ ).

Example 18: *N*-Cyclopentyl-2-[2-(cyclopentylamino)-4-pyridinyl]-3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine.



a) 4-[2-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine. To a cold ( $0^{\circ}\text{C}$ ) solution of 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfonyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (200 mg, 0.59 mmol) in dichloromethane (10 mL) was added *m*-chloroperoxybenzoic acid (154 mg, 70%, 0.62  
 30 mmol). The reaction mixture was warmed to room temperature and stirred 16 hours. The reaction mixture was diluted with dichloromethane and washed with saturated

aqueous sodium bicarbonate solution. The organic layer was concentrated *in vacuo* to provide a green foam, which was dissolved in isopropylamine and heated in a sealed glass pressure tube at 45 °C for 16 hours. The reaction mixture was cooled and the excess isopropylamine was removed under a stream of nitrogen to provide crude 4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine (204 mg, 99%). *R*<sub>f</sub> 0.25 (9:1 dichloromethane:acetone); MS *m/z* 349 (*M*+1).

b) *N*-Cyclopentyl-*N*-(4-{3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-2-yl}-2-pyridinyl)amine.

- 10 A solution of crude 4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine (204 mg, 0.586 mmol) in cyclopentylamine (2 mL, 20.3 mmol) was heated at 135 °C in a sealed glass tube for 16 hours. The reaction mixture was cooled and the excess cyclopentylamine was removed *in vacuo*. The resultant residue was partitioned between ethyl acetate and saturated aqueous sodium
- 15 bicarbonate solution. The organic layer was washed with brine and dried over magnesium sulfate. Filtration and concentration, followed by flash chromatography (1:1 hexanes:ethyl acetate to 100% ethyl acetate) provided *N*-cyclopentyl-*N*-(4-{3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-2-yl}-2-pyridinyl)amine (155 mg, 64%). *R*<sub>f</sub> 0.16 (1:2 hexanes:ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.49 (d, 1H), 8.39 (d, 1H), 8.13-8.08 (m, 2H), 7.29 (t, 1H), 6.89 (t, 1H), 6.80 (d, 1H), 6.63 (s, 1H), 6.46 (d, 1H), 5.23 (br, 1H), 4.86 (d, 1H), 4.21 (m, 1H), 3.93 (m, 1H), 1.95 (m, 2H), 1.70-1.42 (m, 6H), 1.27 (d, 6H); MS *m/z* 414 (*M*+1).

- c) 4-{7-Chloro-2-[2-(cyclopentylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-isopropyl-2-pyrimidinamine.

- In a similar manner as described in Example 17 from *N*-cyclopentyl-*N*-(4-{3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-2-yl}-2-pyridinyl)amine (155 mg, 0.375 mmol), *n*-butyllithium (700 μL, 1.6 M in hexanes, 1.12 mmol), and carbon tetrachloride (145 μL, 1.50 mmol) was formed 4-{7-chloro-2-[2-(cyclopentylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-isopropyl-2-pyrimidinamine. Flash chromatography (1:1 hexanes:ethyl acetate to 1:2 hexanes:ethyl acetate) provided
- 30

sample (65 mg, 39%). R<sub>f</sub> 0.20 (1:1 hexanes:ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.40 (d, 1H), 8.14–8.11 (m, 2H), 7.27 (m, 1H), 7.07 (d, 1H), 6.82 (d, 1H), 6.66 (s, 1H), 6.46 (d, 1H), 5.11 (d, 1H), 4.79 (d, 1H), 4.21 (m, 1H), 3.98 (m, 1H), 1.98 (m, 2H), 1.74–1.44 (m, 6H), 1.30 (d, 6H); MS *m/z* 448 (M+1).

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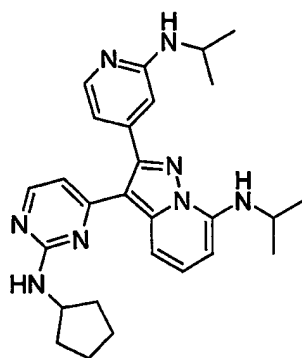
d) *N*-Cyclopentyl-2-[2-(cyclopentylamino)-4-pyridinyl]-3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine.

In a similar manner as described in Example 17 from 4-{7-chloro-2-[2-(cyclopentylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-isopropyl-2-pyrimidinamine (30 mg, 0.067 mmol) and cyclopentylamine (1 mL, 10 mmol) was formed *N*-cyclopentyl-2-[2-(cyclopentylamino)-4-pyridinyl]-3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (2 mg, 6%) as a yellow solid. R<sub>f</sub> 0.22 (1:1 hexanes:ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.09–8.05 (m, 2H), 7.70 (d, 1H), 7.34 (t, 1H), 6.86 (d, 1H), 6.69 (s, 1H), 6.44 (d, 1H), 6.07 (d, 1H), 6.01 (d, 1H), 5.85 (br, 1H), 5.20 (br, 1H), 4.21 (m, 1H), 4.02 (m, 1H), 3.93 (m, 1H), 2.15 (m, 2H), 1.97 (m, 2H), 1.84–1.51 (m, 12 H), 1.29 (d, 6H); MS *m/z* 497 (M+1).

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Example 19: 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine.

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a) *N*-Cyclopentyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine. In a similar manner as described in example 17 from 2-(2-fluoro-4-pyridinyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (410 mg, 1.16 mmol) and cyclopentylamine (4 mL, 40.5 mmol) was formed crude *N*-cyclopentyl-4-[2-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (385 mg), of

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which 260 mg (0.694 mmol) was dissolved in isopropylamine (3 mL, 35.2 mmol) and heated at 150 °C in a steel bomb for 16 hours. The reaction mixture was cooled and the excess isopropylamine was removed under a stream of nitrogen to provide *N*-cyclopentyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine (170 mg, 52% for 2 step procedure) as a beige solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.50 (d, 1H), 8.41 (d, 1H), 8.13-8.08 (m, 2H), 7.32 (t, 1H), 6.92 (t, 1H), 6.80 (d, 1H), 6.62 (s, 1H), 6.47 (d, 1H), 5.26 (d, 1H), 4.63 (d, 1H), 4.34 (m, 1H), 3.85 (m, 1H), 2.11-2.04 (m, 2H), 1.79-1.51 (m, 6H), 1.22 (d, 6H); MS *m/z* 414 (M+1).

- 10 b) 4-{7-Chloro-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-cyclopentyl-2-pyrimidinamine.

In a similar manner as described in Example 17 from *N*-cyclopentyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine (166 mg, 0.401 mmol), *n*-butyllithium (753 μL, 1.6 M in hexanes, 1.20 mmol) and carbon tetrachloride (155 μL, 1.60 mmol) was formed 4-{7-chloro-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-cyclopentyl-2-pyrimidinamine (140 mg, 78%). R<sub>f</sub> 0.21 (1:1 hexanes:ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.36 (d, 1H), 8.19 (d, 1H), 8.07 (d, 1H), 7.36 (m, 1H), 7.13 (d, 1H), 6.90 (d, 1H), 6.81 (s, 1H), 6.52 (d, 1H), 5.25-5.21 (br, 2H), 4.35 (m, 1H), 3.89 (m, 1H), 2.18-2.04 (m, 2H), 1.80-1.50 (m, 6H), 1.22 (d, 6H).

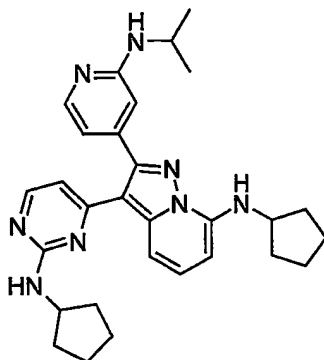
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- c) 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine.

In a similar manner as described in Example 17 from 4-{7-chloro-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-cyclopentyl-2-pyrimidinamine (35 mg, 0.0781 mmol) and isopropylamine (2 mL, 23.5 mmol) was formed 3-[2-(cyclopentylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine (5 mg, 14%) as a yellow solid. R<sub>f</sub> 0.22 (1:1 hexanes:ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.48 (s, 1H), 7.99 (s, 1H), 7.94 (d, 1H), 7.65 (d, 1H), 7.36 (t, 1H), 6.84 (d, 1H), 6.75 (s, 1H), 6.45 (d, 1H), 6.07 (d, 1H), 5.92 (d, 1H), 4.61 (br, 1H), 4.29 (m, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 2.04 (m, 2H), 1.76-1.55 (m, 6H), 1.39 (d, 6H), 1.25 (d, 6H); MS *m/z* 471 (M+1).

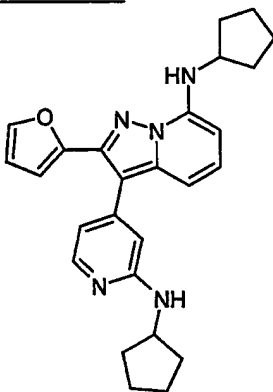
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Example 20: *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine.



In a similar manner as described in Example 17 from 4-{7-chloro-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-*N*-cyclopentyl-2-pyrimidinamine (35 mg, 0.0781 mmol) and cyclopentylamine (2 mL) was formed *N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine (15 mg, 38%). *R*<sub>f</sub> 0.20 (39:1 dichloromethane:methanol); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.13 (d, 1H), 8.03 (d, 1H), 7.72 (d, 1H), 7.30 (t, 1H), 6.80 (d, 1H), 6.60 (s, 1H), 6.42 (d, 1H), 6.03 (d, 1H), 5.99 (d, 1H), 5.13 (d, 1H), 4.51 (d, 1H), 4.32 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 2.15-1.91 (m, 4H), 1.81-1.50 (m, 12H), 1.21 (d, 6H); MS *m/z* 497 (M+1).

Example 21: *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.



## a) 2-(6-Chloro-2-pyridinyl)-1-(2-furyl)ethanone.

The title compound was prepared from ethyl 2-furonate (6.3 g, 45 mmol) and 6-chloropicoline (5.7 g, 45 mmol) as a mixture of ketone and enol tautomers in a similar manner as described in Example 1. The product was purified by silica gel

- 5 chromatography (3:1 hexane:ethyl acetate) to give 2-(6-chloro-2-pyridinyl)-1-(2-furyl)ethanone (4.7g, 47 %) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (s, 1H), 7.82 (t, 1H), 7.57 (d, 1H), 7.39 (d, 2H), 6.73 (m, 1H), 4.35 (s, 2H); MS *m/z* 222 (M+1).

## b) 2-(6-Chloro-2-pyridinyl)-1-(2-furyl)ethanone oxime.

- 10 The title compound was prepared from 2-(6-chloro-2-pyridinyl)-1-(2-furyl)ethanone (4.5 g, 20 mmol) in a similar manner as described in example 1. The product was purified by silica gel chromatography (4:1 hexane:ethyl acetate) to give 2-(6-chloro-2-pyridinyl)-1-(2-furyl)ethanone oxime (2.7 g, 56 %) as a solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.4 (s, 1H), 7.76-7.70 (m, 2H), 7.31 (d, 1H), 7.19 (d, 1H), 6.75 (m, 1H), 6.52 (m, 1H), 4.1 (s, 2H); MS *m/z* 237 (M+1).
- 15

c) 7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine.

- The title compound was prepared from 2-(6-chloro-2-pyridinyl)-1-(2-furyl)ethanone oxime (2.7 g, 11 mmol) in a similar manner as described in example 1. The product was
- 20 purified by silica gel chromatography (6:1 hexane:ethyl acetate) to give 1 g (40 %) of 7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (broad s, 1H), 7.49 (d, 1H), 7.08 (dd, 1H), 6.95 (d, 1H), 6.90 (d, 1H), 6.86 (s, 1H), 6.51 (dd, 1H); MS *m/z* 219 (M+1).

- 25 d) 3-Bromo-7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine.

- 7-Chloro-2-(2-furyl)-pyrazolo[1,5-*a*]pyridine (0.23 g, 1.05 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to 0°C. N-Bromosuccinimide (0.19 g, 1.05 mmol) was added. The reaction was stirred for 1 hour. The reaction solution was poured into equal volumes (10 mL) of saturated aqueous ammonium chloride and ether. The ether
- 30 layer was collected and the solvent removed *in vacuo* to give the crude product. The product was purified by silica gel chromatography (6:1 hexane:ethyl acetate) to give

0.3 g (96 %) of 3-bromo-7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.63 (d, 1H), 7.51 (d, 1H), 7.29 (d, 1H), 7.21 (dd, 1H), 6.98 (d, 1H), 6.58 (dd, 1H); MS *m/z* 298 (M+1).

5 e) *N*-[3-Bromo-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-yl]-*N*-cyclopentylamine.

3-Bromo-7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine (0.3 g, 1 mmol) was dissolved in toluene (10 mL). 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.048 g, 0.06 mmol), palladium(II)acetate (0.01 g, 0.04 mmol) and cesium carbonate (0.82 g, 2.6 mmol) was added. Cyclopropylamine (0.5 mL) was added and the reaction was heated in an 85°C  
10 oil bath for 4 hours. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.048 g, 0.06 mmol), and palladium(II)acetate (0.01 g, 0.04 mmol) were added again and the reaction heated in a 105°C oil bath for 4 hours. The reaction mixture was poured into equal volumes (10 mL) of saturated aqueous ammonium chloride and ether. The ether layer was collected and the solvent removed *in vacuo* to give the crude product. The  
15 product was purified by silica gel chromatography (6:1hexane:ethyl acetate) to give 0.25 g (72 %) of *N*-[3-bromo-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-yl]-*N*-cyclopentylamine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.6 (broad s, 1H), 7.24 (1H), 7.10 (m, 1H), 6.86 (m, 1H), 6.57 (m, 1H), 5.94 (m, 1H), 4.0 (m, 1H), 2.19-2.09 (m, 2H); 1.88-1.77 (m, 4H), 1.77-1.64 (m, 2H); MS *m/z* 345, 348 (M+1).

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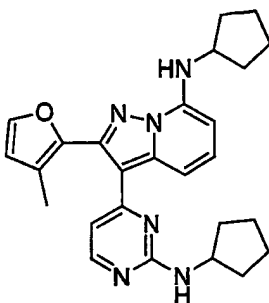
f) 2-Fluoropyridin-4-ylboronic acid.

To a stirred solution of *n*-butyl lithium (3.2 mL, 2.5M, 8.0 mmol) in dry diethyl ether (20 mL) at -78°C was added a solution of 2-fluoro-4-iodopyridine (1.5 g, 6.7 mmol) in dry ether (10 mL) and the reaction mixture was stirred at -78°C for 10 minutes.  
25 Tributyl borate (2.4 mL, 2.01 g, 8.7 mmol) was added and the reaction mixture was allowed to warm to room temperature over 2 hours. Water (5 mL) was added followed by 2N aqueous sodium hydroxide solution (10 mL) to dissolve the solids. The organic phase was separated. The aqueous phase was acidified to pH 3 using 6N hydrochloric acid and the resulting white solid was collected by filtration and dried under vacuum  
30 to give the title compound, 0.74 g (78%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.65 (broad s, 2H), 8.21 (d, 1H), 7.59 (t, 1H), 7.37 (d, 1H).

- g) *N*-Cyclopentyl-3-(2-fluoro-4-pyridinyl)-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine. *N*-[3-Bromo-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-yl]-*N*-cyclopentylamine (0.2 g, 0.6 mmol) was dissolved in *N,N*-dimethylformamide (8 mL). To this solution was added 2-fluoro-4-pyridinylboronic acid (0.09 g, 0.64 mmol), dichlorobis(triphenylphosphine)-palladium (II) (0.020 g, 0.03 mmol) and saturated aqueous sodium carbonate (580  $\mu$ l). The resulting solution was heated in a 75°C oil bath overnight. Water was added to the reaction mixture and the product was extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated to a solid. The product was purified by silica gel chromatography (7:1 hexane:ethyl acetate) to give 50 mg (24 %) of *N*-cyclopentyl-3-(2-fluoro-4-pyridinyl)-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.1 (d, 1H), 7.5 (s, 1H), 7.24 (1H), 7.03 (s, 1H), 6.96 (d, 1H), 6.75 (d, 1H), 6.5 (m, 1H), 6.01 (m, 2H), 4.0 (m, 1H), 2.19-2.09 (m, 2H); 1.88-1.77 (m, 4H), 1.77-1.64 (m, 2H); MS *m/z* 363 (M+1).
- h) *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine. *N*-Cyclopentyl-3-(2-fluoro-4-pyridinyl)-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine (0.05 g, 0.02 mmol) was dissolved in cyclopentylamine (1 mL and heated) in a 135 °C oil bath for 4 days. The amine was removed *in vacuo*. The product was purified by silica gel chromatography (7:1 hexane:ethyl acetate) to give 25 mg (42 %) of *N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.1 (d, 1H), 7.51 (s, 1H), 7.17 (t, 1H), 6.94 (d, 1H), 6.69 (m, 2H), 6.5 (s, 1H), 6.45 (m, 1H), 6.00 (d, 1H), 5.95 (d, 1H), 4.6 (br d, 1H), 4.0 (m, 1H), 3.92 (m, 1H), 2.19-2.09 (m, 2H), 2.03-1.95 (m, 2H), 1.88-1.43 (m, 8H), 1.32-1.22 (m, 2H); MS *m/z* 428 (M+1).

Example 22: N-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-a]pyridin-7-amine.

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a) 2-(6-Chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone.

To a cold (0 °C) solution of 6-chloro-2-picoline (25.8 mL, 236 mmol) and methyl 3-methyl-2-furoate (33.08 g, 236 mmol) in tetrahydrofuran (300 mL) was added lithium bis(trimethylsilyl)amide (472 mL, 1.0 M in tetrahydrofuran, 472 mmol) dropwise *via* a pressure equalizing funnel over 1 hour. Upon complete addition, the cold bath was removed and the resultant solution was stirred at room temperature for 15 hours. The solution was concentrated. Methanol was added to quench the reaction resulting in a yellow solid precipitating. The precipitate was collected by filtration and washed with a small amount of cold methanol. 2-(6-Chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone (52.2 g, 94%) was obtained as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.61 (t, 1H), 7.43 (s, 1H), 7.23 (m, 2H), 6.40 (s, 1H), 4.36 (s, 2H), 2.37 (s, 3H). MS *m/z* 236 (M+1).

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b) 2-(6-Chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone oxime.

To a solution of 2-(6-chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone (52.2 g, 221 mmol) in methanol (500 mL) was added hydroxylamine hydrochloride (76.96 g, 1.11 mol) followed by an aqueous solution of sodium hydroxide (44.3 g, 1.11 mol). The resultant suspension was heated at reflux for 2 hours and then cooled to room temperature. The mixture was concentrated and water was added to the residue while stirring. After stirring for 20 minutes, a white solid precipitated. This solid was collected by filtration and washed with water to give 2-(6-chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone oxime (29.0 g, 52%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.54

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(t, 1H), 7.31 (s, 1H), 7.15 (d, 1H), 7.10 (d, 1H), 6.28 (s, 1H), 4.34 (s, 2H), 2.22 (s, 3H). MS  $m/z$  273 (M+1).

c) 7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridine.

- 5 To a solution of 2-(6-chloro-2-pyridinyl)-1-(3-methyl-2-furyl)ethanone oxime (24.5 g, 97.7 mmol) in 1,2-dimethoxyethane (200 mL) at 0 °C was added trifluoroacetic anhydride (14.5 mL, 103 mmol), while keeping the temperature below 10 °C. After the addition was complete, the reaction was warmed to 15 °C. The solution was then cooled to 0-5 °C and a solution of triethylamine (28.6 mL, 205 mmol) in 1,2-
- 10 dimethoxyethane (30 mL) was added over 0.5 hours. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. To this mixture was added iron(II) chloride (0.62 g, 4.9 mmol) and the reaction was heated at 75 °C for 15 hours. The reaction was concentrated, then ethyl acetate and water were added. The organic phase was separated, washed with water, dried (magnesium sulfate),
- 15 filtered and concentrated. Purification by silica gel chromatography (9:1 hexanes:ethyl acetate) gave 7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridine (14.6 g, 64%) as yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.52 (d, 1H), 7.48 (d, 1H), 7.10 (t, 1H), 6.92 (d, 1H), 6.86 (s, 1H), 6.42 (d, 1H), 2.49 (s, 3H). MS  $m/z$  233 (M+1).

- 20 d) 7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde.

- A dry flask charged with dry *N,N*-dimethylformamide (100 mL) was treated with phosphorous oxychloride (8.8 mL, 94 mmol). The resultant solution was stirred at room temperature for 1 hour. 7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridine (14.6 g, 63 mmol) was added and the reaction mixture was stirred for 2.5 hours.
- 25 Water and dichloromethane were added to quench the reaction. The aqueous phase and organic phase were separated. The aqueous phase was extracted with dichloromethane. The organics were combined and washed with water, dried over magnesium sulfate, filtered and the filtrate was concentrated. Crystallization from a small amount of methanol gave 7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-
- 30 *a*]pyridine-3-carbaldehyde (12.4 g, 76%) as a peach color crystalline compound. <sup>1</sup>H

NMR (CDCl<sub>3</sub>):  $\delta$  10.58 (s, 1H), 8.43 (d, 1H), 7.58 (d, 1H), 7.48 (t, 1H), 7.21 (d, 1H), 6.51 (d, 1H), 2.56 (s, 3H). MS  $m/z$  261 (M+1).

e) 1-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol.

- 5 To a solution of 7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (11.56 g, 44.3 mmol) in tetrahydrofuran (200 mL) at -78 °C was added ethynylmagnesium bromide (133 mL, 0.5 M in tetrahydrofuran, 66.5 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hour. Water was added to the reaction and the resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was dried over magnesium sulfate, filtered and concentrated to a solid residue, 1-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (12.29 g, 97%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.97 (d, 1H), 7.48 (d, 1H), 7.16 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 6.18 (m, 1H), 2.78 (m, 1H), 2.6 (d, 1H), 2.46 (s, 3H). MS  $m/z$  287 (M+1).

15

f) 1-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one.

- 1-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (12.29 g, 42.9 mmol) was dissolved in dichloromethane (200 mL) and manganese dioxide (112 g, 1.29 mol) was added. This slurry was stirred at room temperature for 2 hours. The manganese dioxide was removed by filtration and the filtrate was concentrated to a solid. This solid was purified by flash chromatography (dichloromethane) to give 1-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (7.53 g, 62%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  8.37 (d, 1H), 7.48 (m, 2H), 7.19 (d, 1H), 6.41 (d, 1H), 3.12 (s, 1H), 2.20 (s, 3H). MS  $m/z$  285 (M+1).

25

g) 4-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine.

- Sodium ethylate solution (21% T, 0.5 mL, 1.43 mmol) was added to ethanol followed by cyclopentylguanidine hydrochloride (323 mg, 1.98 mmol). The mixture was stirred at room temperature for 30 minutes. 1-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (313 mg, 1.10 mmol) was added to the resultant

30

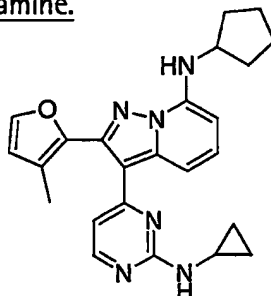
solution and stirred at room temperature for 15 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue. The phases were separated, the organic phase dried (magnesium sulfate), filtered and concentrated. The residue was recrystallized from ethyl acetate. 4-[7-Chloro-2-(3-methyl-2-

- 5 furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (280 mg, 65%) was obtained as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.50 (d, 1H), 8.15 (d, 1H), 7.49 (d, 1H), 7.27 (t, 1H), 7.06 (d, 1H), 6.41 (d, 1H), 6.36 (d, 1H), 5.10 (d, 1H), 4.35 (m, 1H), 2.12 (s, 3H), 2.08 (m, 2H), 1.78-1.53 (m, 6H). MS *m/z* 394 (M+1).

- 10 h) *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.

- To a solution of 4-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (150 mg, 0.38 mmol) in cyclopentylamine (10 mL) was added *racemic*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (76 mg, 0.12 mmol),  
15 cesium carbonate (247 mg, 0.76 mmol) and palladium (II) acetate (17 mg, 0.076 mmol). The resulting mixture was stirred at 100 °C for 3 hours. Water was added and the mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (3:7 ethyl acetate:hexane) to  
20 give 147 mg (87%) of *N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.07 (d, 1H), 7.85 (d, 1H), 7.50 (d, 1H), 7.31 (t, 1H), 6.42 (d, 1H), 6.25 (d, 1H), 6.04 (d, 1H), 6.00 (d, 1H), 5.06 (d, 1H), 4.36 (m, 1H), 3.98 (m, 1H), 2.08 (m, 4H), 2.05 (s, 3H), 1.81-1.52 (m, 12 H). MS *m/z* 443 (M+1).

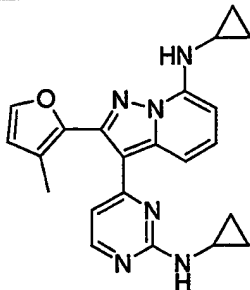
Example 23: *N*-Cyclopentyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.



a) 4-[7-Chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopropyl-2-pyrimidinamine. In a similar manner described in Example 22 from 1-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (500 mg, 1.76 mmol) was obtained 4-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopropyl-2-pyrimidinamine (182 mg, 28%) as a pale yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.66 (broad d, 1H), 8.18 (d, 1H), 7.48 (d, 1H), 7.22 (t, 1H), 7.03 (d, 1H), 6.41 (m, 2H), 5.75 (s, 1H), 2.81 (m, 1H), 2.12 (s, 3H), 0.80 (m, 2H), 0.59 (m, 2H). MS *m/z* 366 (M+1).

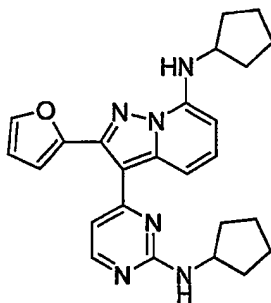
b) *N*-Cyclopentyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine. In the similar manner as described in Example 22 from 4-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopropyl-2-pyrimidinamine (80 mg, 0.22 mmol) was obtained *N*-cyclopentyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine (20 mg, 21%) as a yellow foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.12 (d, 1H), 8.01 (d, 1H), 7.51 (d, 1H), 7.31 (t, 1H), 6.43 (d, 1H), 6.32 (d, 1H), 6.05 (d, 1H), 6.00 (d, 1H), 5.35 (s, 1H), 4.00 (m, 1H), 2.87 (m, 1H), 2.13 (m, 2H), 2.06 (s, 3H), 1.81-1.66 (m, 6H), 0.86 (m, 2H), 0.62 (m, 2H). MS *m/z* 415 (M+1).

Example 24: *N*-Cyclopropyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.



In a similar manner as described in Example 22 from 4-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopropyl-2-pyrimidinamine (92 mg, 0.25 mmol) was obtained *N*-cyclopropyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine (75 mg, 77%) as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.17 (d, 1H), 8.12 (d, 1H), 7.54 (d, 1H), 7.38 (t, 1H), 6.46-6.36 (m, 4H), 5.44 (s, 1H), 2.89 (m, 1H), 2.70 (m, 1H), 2.09 (s, 3H), 0.91 (m, 4H), 0.77 (m, 2H), 0.66 (m, 2H). MS *m/z* 387 (M+1).

Example 25: *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine



a) 7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde.

A dry flask charged with dry *N,N*-dimethylformamide (100 mL) was treated with phosphorous oxychloride (6.0 mL, 64.5 mmol). The resultant solution was stirred at room temperature for 1 hour. 7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine (9.4 g, 43 mmol, example 21) was added to the previous solution and stirred for 2.5 hours. Water and dichloromethane were added to quench the reaction. The aqueous phase and organic phase were separated. The aqueous phase was extracted with dichloromethane. The organics were combined and washed with water, dried over

magnesium sulfate, filtered and concentrated. Crystallization from a small amount of methanol gave 7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (8.4 g, 79%) as pale yellow crystalline compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.57 (s, 1H), 8.41 (d, 1H), 7.71 (d, 1H), 7.51 (t, 1H), 7.27 (d, 1H), 7.22 (d, 1H), 6.66 (m, 1H). MS *m/z* 247 (M+1).

b) 1-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol.

To a solution of 7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (3.36 g, 13.6 mmol) in tetrahydrofuran (100 mL) at -78 °C was added ethynylmagnesium bromide (32.7 mL, 0.5 M in tetrahydrofuran, 16.3 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hour. Water was added to the reaction and the resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was dried over magnesium sulfate, filtered and concentrated to a solid residue, 1-[7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (3.63 g, 98%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.98 (d, 1H), 7.59 (d, 1H), 7.16 (t, 1H), 7.03 (d, 1H), 6.95 (d, 1H), 6.55 (m, 1H), 6.16 (m, 1H), 2.76 (m, 1H), 2.63 (s, 1H). MS *m/z* 273 (M+1).

c) 1-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one.

1-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (3.63 g, 13.3 mmol) was dissolved in dichloromethane (200 mL) and manganese dioxide (34.7 g, 399 mmol) was added. This slurry was stirred at room temperature for 2 hours. The manganese dioxide was removed by filtration and the filtrate was concentrated to a solid, 1-[7-chloro-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (1.99 g, 55%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.54 (d, 1H), 7.65 (d, 1H), 7.62 (d, 1H), 7.49 (t, 1H), 7.21 (d, 1H), 6.58 (m, 1H), 3.35 (s, 1H). MS *m/z* 271 (M+1).

d) 4-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine.

Cyclopentylguanidine hydrochloride (1.53 g, 9.38 mmol) and potassium carbonate (0.78g, 5.63 mmol) were added to 80 mL of ethanol. The suspension was stirred at room temperature for 1 hour. 1-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-

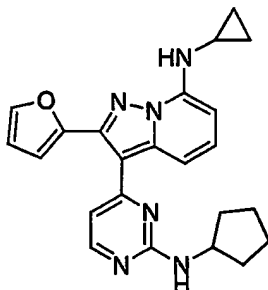
propyn-1-one (1.27 g, 4.69 mmol) was added to the resultant solution and stirred at room temperature for 24 hours. The reaction mixture was concentrated and ethyl acetate and water were added. The phases were separated, the organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (3:7 ethyl acetate:hexanes) gave 4-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (520 mg, 30%) as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.28 (d, 1H), 8.22 (d, 1H), 7.58 (d, 1H), 7.23 (m, 1H), 7.04 (d, 1H), 6.92 (d, 1H), 6.62 (d, 1H), 6.53 (m, 1H), 5.16 (d, 1H), 4.35 (m, 1H), 2.07 (m, 2H), 1.77-1.52 (m, 6H). MS *m/z* 380 (M+1).

e) *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.

4-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (200 mg, 0.53 mmol) was dissolved in 5 mL of cyclopentylamine. The solution was heated at 100 °C overnight, then cooled to room temperature. Ethyl acetate was added to dilute the reaction mixture, the organic phase was washed with water and brine and dried over magnesium sulfate. Filtration and concentration followed by purification with flash chromatography (1:4 ethyl acetate:hexanes) gave *N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine (206 mg, 91%) as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.20 (d, 1H), 7.68 (d, 1H), 7.62 (d, 1H), 7.32 (t, 1H), 6.92 (d, 1H), 6.59 (m, 2H), 6.05 (m, 2H), 5.11 (d, 1H), 4.43 (m, 1H), 4.04 (m, 1H), 2.14 (m, 4H), 1.87-1.56 (m, 12H). MS *m/z* 429 (M+1).

Example 26: 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-N-cyclopropyl-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine.

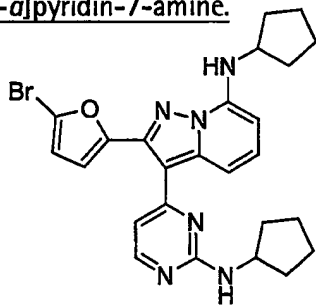
5



- 10 4-[7-Chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-3-yl]-N-cyclopentyl-2-pyrimidinamine (100 mg, 0.26 mmol) and cyclopropylamine (5 mL) were put in a steel bomb. After heating at 100°C for 3 days, the reaction was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, then dried over magnesium sulfate. Filtration and concentration followed by
- 15 purification with flash chromatography (3:7 ethyl acetate:hexanes) gave 3-[2-(cyclopentylamino)-4-pyrimidinyl]-N-cyclopropyl-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine (34 mg, 32%) as a yellow foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.15 (d, 1H), 7.67 (d, 1H), 7.56 (d, 1H), 7.30 (t, 1H), 6.86 (d, 1H), 6.57 (d, 1H), 6.52 (m, 1H), 6.36 (d, 1H), 6.32 (s, 1H), 5.14 (d, 1H), 4.36 (m, 1H), 2.63 (m, 1H), 2.08 (m, 2H), 1.76-1.52 (m, 6H), 0.86 (m, 2H), 0.75 (m, 2H). MS *m/z* 401 (M+1).
- 20

Example 27: 2-(5-Bromo-2-furyl)-N-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine.

25



- 30 a) 2-(5-Bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridine-3-carbaldehyde.

To a solution of 7-chloro-2-(2-furyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (2.0 g, 8.06 mmol) in dichloromethane was added *N*-bromosuccinimide (2.01 g, 11.28 mmol). After stirring at room temperature for 2 hours, the reaction mixture was diluted with dichloromethane, washed with water and brine and dried over magnesium sulfate.

5 Filtration and concentration followed by recrystallization with ethyl acetate gave 2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridine-3-carbaldehyde (2.1 g, 80%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.50 (s, 1H), 8.37 (dd, 1H), 7.47 (t, 1H), 7.20-7.18 (m, 2H), 6.54 (d, 1H). MS *m/z* 325 (M+1).

10 b) 1-[2-(5-Bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one. In a similar manner as described in Example 25 from 2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridine-3-carbaldehyde (2.54 g, 7.8 mmol) was obtained 1-[2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol. To the solution of 1-[2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol in dichloromethane was added manganese dioxide as described in example 25. 1-[2-(5-Bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (0.86 g, two steps 32%) was obtained as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.53 (d, 1H), 7.52-7.48 (m, 2H), 7.22 (d, 1H), 6.51 (d, 1H), 3.36 (s, 1H). MS *m/z* 349 (M+1).

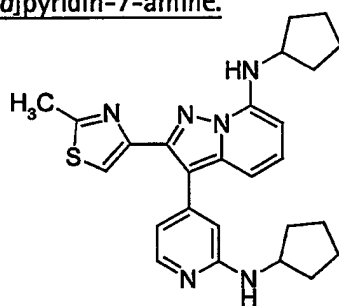
20 c) 4-[2-(5-Bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine. In a similar manner as described in example 25 from 1-[2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (0.85 g, 2.43 mmol) was obtained 4-[2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (0.81 g, 73%) as a pale yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  
25 δ 8.24 (m, 2H), 7.25 (t, 1H), 7.05 (dd, 1H), 6.88 (d, 1H), 6.66 (d, 1H), 6.46 (d, 1H), 5.15 (d, 1H), 4.35 (m, 1H), 2.07 (m, 2H), 1.77-1.52 (m, 6H). MS *m/z* 458 (M+1).

d) 2-(5-Bromo-2-furyl)-*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine. In a similar manner as described in  
30 example 25 from 4-[2-(5-bromo-2-furyl)-7-chloropyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (200 mg, 0.56 mmol) was obtained 2-(5-bromo-2-

furyl)-*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (190 mg, 86%) as a yellow foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.16 (d, 1H), 7.56 (d, 1H), 7.28 (t, 1H), 6.83 (d, 1H), 6.62 (d, 1H), 6.45 (d, 1H), 6.04 (d, 1H), 6.01 (d, 1H), 5.20 (b, 1H), 4.37 (m, 1H), 4.00 (m, 1H), 2.18–2.04 (m, 4H), 1.84–1.55 (m, 12H). MS *m/z* 507 (M+1).

Example 28: *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-7-amine.

10



15 a) 4-(2-Fluoro-4-pyridinyl)-3-butyne-2-ol.

A solution of 2-fluoro-4-iodopyridine (3.0 g, 13 mmol), 3-butyne-2-ol (2.1 mL, 26 mmol), dichlorobis(triphenylphosphine) palladium (II) (0.9 g, 1.3 mmol), copper (I) iodide (0.5 g, 2.6 mmol), triethylamine (5.4 mL, 39 mmol), and anhydrous *N,N*-dimethylformamide (20 mL) were heated to 75 °C for 4 hours. When judged to be complete, the mixture was partitioned between ethyl acetate and water, the organics were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude mixture was purified using flash chromatography (4:1 hexanes: ethyl acetate) to provide 4-(2-fluoro-4-pyridinyl)-3-butyne-2-ol (1.4 g, 66%) as an orange oil. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.21 (d, 1H), 7.32 (d, 1H), 7.20 (s, 1H), 5.62 (d, 1H), 4.61 (m, 1H), 1.36 (d, 3H).

b) 1-[3-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanol.

A solution of 4-(2-fluoro-4-pyridinyl)-3-butyne-2-ol (1.4 g, 8.5 mmol), aminopyridinium iodide (2.2 g, 9.8 mmol), 1,8-diazobicyclo[5.4.0]undec-7-ene (1.9 mL, 12.7 mmol), and acetonitrile (20 mL) were allowed to stir for 12–16 hours at room temperature. When judged to be complete, the mixture was partitioned between ethyl acetate and water, the organics were washed with brine, dried over magnesium

sulfate, filtered and suspended onto silica gel. The crude material was purified by flash chromatography (1:1 hexanes : ethyl acetate) to provide 1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanol (1.0 g, 46%) as a beige solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.79 (d, 1H), 8.30 (d, 1H), 7.87 (d, 1H), 7.67 (d, 1H), 7.50 (s, 1H), 7.41 (m, 1H), 7.04 (m, 1H), 5.57 (m, 1H), 5.03 (m, 1H), 1.56 (d, 3H).

c) 1-[3-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone.

A solution of 1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanol (0.1 g, 0.4 mmol), manganese(IV)oxide (0.17 g, 1.95 mmol), and methylene chloride (10 mL) were allowed to stir at room temperature for 72 hours. When judged to be complete, the mixture was filtered through a plug of Celite, and the filtrate was concentrated to provide 1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone (97 mg, 98%) as a pale yellow solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.92 (d, 1H), 8.30 (d, 1H), 7.82 (d, 1H), 7.46 (m, 2H), 7.34 (s, 1H), 7.23 (m, 1H), 2.71 (s, 3H).

d) 2-Bromo-1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone.

To a solution of 1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone (580 mg, 2.27 mmol) in acetic acid (20 mL) was added bromine (0.12 mL, 2.27 mmol). After heating at 80 °C for 30 minutes, the solution was cooled to room temperature. Ethyl acetate was added to dilute the reaction mixture. The mixture was washed with water (x3), brine and dried over magnesium sulfate. Filtration and concentration, followed by recrystallization from ethyl acetate gave 2-bromo-1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone (478 mg, 64 %) as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.51 (d, 1H), 8.27 (d, 1H), 7.65 (d, 1H), 7.33 (m, 2H), 7.10 (s, 1H), 7.06 (t, 1H), 4.76 (s, 2H). MS *m/z* 334 (M+1).

e) 3-(2-Fluoro-4-pyridinyl)-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridine.

To a solution of 2-bromo-1-[3-(2-fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-2-yl]ethanone (250 mg, 0.75 mmol) in *N,N*-dimethylformamide (15 mL) was added thioacetamide (67 mg, 0.90 mmol). After heating at 60 °C for 3 hours, the reaction was cooled to room temperature. An ammonium hydroxide solution was used to

adjust the pH to 9. The resultant solution was extracted with ethyl acetate. The organics were combined and washed with water, brine and dried over magnesium sulfate. Filtration and concentration gave 3-(2-fluoro-4-pyridinyl)-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridine (220 mg, 95 %) as a pale yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.56 (d, 1H), 8.23 (d, 1H), 7.61 (d, 1H), 7.30 (s, 1H), 7.27 (m, 2H), 7.05 (s, 1H), 6.89 (m, 1H), 2.76 (s, 3H). MS *m/z* 311 (M+1).

f) *N*-Cyclopentyl-4-[2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyridinamine.

10 A solution of 3-(2-fluoro-4-pyridinyl)-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridine (220 mg, 0.71 mmol) and potassium carbonate (98 mg, 0.71 mmol) in cyclopentylamine (5 mL) was heated at 100 °C for 12 days. After cooling to room temperature, the solution was diluted with ethyl acetate and the organic phase was washed with water and brine, then dried over magnesium sulfate. Filtration and  
15 concentration, followed by flash chromatography (1:9 methanol/chloroform) gave *N*-cyclopentyl-4-[2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyridinamine (265 mg, 100%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.49 (d, 1H), 8.04 (d, 1H), 7.49 (d, 1H), 7.08 (t, 1H), 6.74 (t, 1H), 6.59 (d, 1H), 6.43 (s, 1H), 5.44 (d, 1H), 3.79 (m, 1H), 2.73 (s, 3H), 1.92-1.42 (m, 8H). MS *m/z* 376 (M+1).

20

g) 4-[7-Chloro-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyridinamine.

A solution of *N*-cyclopentyl-4-[2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyridinamine (138 mg, 0.37 mmol) in tetrahydrofuran (10 mL) was cooled to -  
25 78 °C. *n*-Butyl lithium (1.6M in hexanes, 0.75 mL, 1.22 mmol) was added dropwise. After stirring at -78 °C for 20 minutes, carbon tetrachloride (1 mL) was added to the solution. The reaction was stirred for another 20 minutes at -78 °C and subsequently quenched with water. The reaction mixture was warmed to room temperature and extracted with ethyl acetate. The organics were combined and washed with water,  
30 brine and dried over magnesium sulfate. Filtration and concentration, followed by flash chromatography (1:19 methanol/dichloromethane) gave 4-[7-chloro-2-(2-

methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyridinamine as a brown oil.

h) *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-7-amine.

To 4-[7-chloro-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyridinamine from previous reaction was added cyclopentylamine and the resulting mixture heated to 80 °C for 3 days. The resultant solution was cooled to room temperature, diluted with ethyl acetate and washed with water, brine and dried over magnesium sulfate. Filtration and concentration followed by flash chromatography (1:19 methanol/dichloromethane) gave *N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-7-amine (20 mg, 12% for two steps) as a brown foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.09 (d, 1H), 7.56 (d, 1H), 7.34 (s, 1H), 7.15 (t, 1H), 6.98 (d, 1H), 6.64 (d, 1H), 6.45 (s, 1H), 5.60 (d, 1H), 4.80 (b, 1H), 3.94 (m, 1H), 3.87 (m, 1H), 2.76 (s, 3H), 1.98-1.45 (m, 16 H). MS *m/z* 459 (M+1).

#### Example 29: Biological Activity

In the following example, "MEM" means Minimal Essential Media; "FBS" means Fetal Bovine Serum; "NP40" and "Igepal" are detergents; "MOI" means Multiplicity of Infection; "NaOH" means sodium hydroxide; "MgCl<sub>2</sub>" means magnesium chloride; "dATP" means deoxyadenosine 5' triphosphate; "dUTP" means deoxyuridine 5' triphosphate; "dCTP" means dexoxycytidine 5' triphosphate; "dGTP" means deoxyguanosine 5' triphosphate; "GuSCN" means Guanidinium thiocyanate; "EDTA" means ethylenediamine tetraacetic acid; "TE" means Tris-EDTA; "SCC" means sodium chloride/sodium citrate; "APE" means a solution of ammonia acetate, ammonia phosphate, EDTA; "PBS" means phosphate buffered saline; and "HRP" means horseradish peroxidase.

a) Tissue Culture and HSV infection.

Vero 76 cells were maintained in MEM with Earle's salts, L-glutamine, 8% FBS (Hyclone, A-1111-L) and 100 units/mL Penicillin-100 µg/mL Streptomycin. For assay conditions, FBS was reduced to 2%. Cells are seeded into 96-well tissue culture plates at a density of  $5 \times 10^4$  cells/well after being incubated for 45 min at 37°C in the presence of HSV-1 or HSV-2 (MOI =0.001). Test compounds are added to the wells and the plates are incubated at 37°C for 40- 48 hours. Cell lysates are prepared as follows: media was removed and replaced with 150 µL/well 0.2 N NaOH with 1% Igepal CA 630 or NP-40. Plates were incubated up to 14 days at room temperature in a humidified chamber to prevent evaporation.

(b) Preparation of detection DNA.

For the detection probe, a gel-purified, digoxigenin-labeled, 710-bp PCR fragment of the HSV UL-15 sequence was utilized. PCR conditions included 0.5 µM primers, 180 µM dTTP, 20 µM dUTP-digoxigenin (Boehringer Mannheim 1558706), 200 µM each of dATP, dCTP, and dGTP, 1X PCR Buffer II (Perkin Elmer), 2.5 mM MgCl<sub>2</sub>, 0.025 units/µL of AmpliTaq Gold polymerase (Perkin Elmer), and 5 ng of gel-purified HSV DNA per 100 µL. Extension conditions were 10 min at 95°C, followed by 30 cycles of 95°C for 1 min, 55°C for 30 sec, and 72°C for 2 min. The amplification was completed with a 10-min incubation at 72°C. Primers were selected to amplify a 728 bp probe spanning a section of the HSV1 UL15 open reading frame (nucleotides 249-977). Single-stranded transcripts were purified with Promega M13 Wizard kits. The final product was mixed 1:1 with a mixture of 6 M GuSCN, 100 mM EDTA and 200 µg/mL herring sperm DNA and stored at 4°C.

(c) Preparation of capture plates.

The capture DNA plasmid (HSV UL13 region in pUC) was linearized by cutting with Xba I, denatured for 15 min at 95°C and diluted immediately into Reacti-Bind DNA Coating Solution (Pierce, 17250, diluted 1:1 with TE buffer, pH 8) at 1 ng/µL. 75 µL/well were added to Corning (#3922 or 9690) white 96-well plates and incubated at room temperature for at least 4 hrs before washing twice with 300 µL/well 0.2X

SSC/0.05% Tween-20 (SSC/T buffer). The plates were then incubated overnight at room temperature with 150  $\mu$ L/well 0.2 N NaOH, 1% IGEPAL and 10  $\mu$ g/mL herring sperm DNA.

5 (d) Hybridization.

Twenty-seven (27)  $\mu$ L of cell lysate was combined with 45  $\mu$ L of hybridization solution (final concentration: 3M GuSCN, 50 mM EDTA, 100  $\mu$ g/ml salmon sperm DNA, 5X Denhardt's solution, 0.25X APE, and 5 ng of the digoxigenin-labeled detection probe). APE is 1.5 M  $\text{NH}_4$ -acetate, 0.15 M ammonium phosphate monobasic, and 5 mM EDTA adjusted to pH 6.0. Mineral oil (50  $\mu$ L) was added to prevent evaporation. The hybridization plates were incubated at 95°C for 10 minutes to denature the DNA, then incubated at 42°C overnight. The wells were washed 6X with 300  $\mu$ L/well SSC/T buffer then incubated with 75  $\mu$ L/well anti-digoxigenin- HRP-conjugated antibody (Boehringer Mannheim 1207733, 1:5000 in TE) for 30 min at room temperature. The wells were washed 6X with 300  $\mu$ L/well with PBS/0.05% Tween-20 before 75  $\mu$ L/well SuperSignal LBA substrate (Pierce) was added. The plates were incubated at room temperature for 30 minutes and chemiluminescence was measured in a Wallac Victor reader.

20 e) Results.

The following results were obtained for HSV-1.

Example No.	IC <sub>50</sub> ( $\mu$ M)
1	1.5
3	0.6
4	3.1
6	0.4
8	0.8
9	23
10	33
11	1.6
12	36

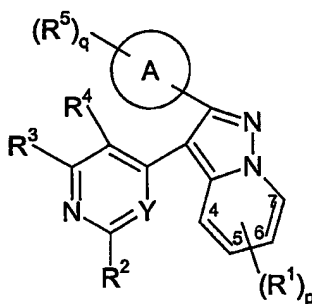
Example No.	IC <sub>50</sub> (μM)
13	3.3
17	2.9
18	1
19	0.7
20	0.5
21	0.5
22	0.2
23	0.8
24	5
25	0.5
26	1.4
27	0.5
28	1.7

The results demonstrate that the compounds of the present invention are useful for the treatment and prophylaxis of herpes viral infections.

## CLAIMS:

1. A compound of formula (I):

5



I

wherein:

- 10 p is 0, 1, 2, 3 or 4;

each R<sup>1</sup> is the same or different and is independently selected from the group

- consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het, -OR<sup>7</sup>,  
 -OAY, -OR<sup>10</sup>AY, -OHet, -OR<sup>10</sup>Het, -C(O)R<sup>9</sup>, -C(O)AY, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>,  
 -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>AY, -C(O)NHR<sup>10</sup>AY, -C(O)NHR<sup>10</sup>Het, -C(S)NR<sup>9</sup>R<sup>11</sup>,  
 15 -C(NH)NR<sup>7</sup>R<sup>8</sup>, -C(NH)NR<sup>7</sup>AY, -S(O)<sub>n</sub>R<sup>9</sup>, -S(O)<sub>n</sub>AY, -S(O)<sub>n</sub>Het, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>,  
 -S(O)<sub>2</sub>NR<sup>7</sup>AY, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>AY, -NHHet, -NHR<sup>10</sup>AY, -NHR<sup>10</sup>Het, -R<sup>10</sup>cycloalkyl,  
 -R<sup>10</sup>AY, -R<sup>10</sup>Het, -R<sup>10</sup>O-C(O)R<sup>9</sup>, -R<sup>10</sup>O-C(O)AY, -R<sup>10</sup>O-C(O)Het, -R<sup>10</sup>O-S(O)<sub>n</sub>R<sup>9</sup>,  
 -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(O)NR<sup>7</sup>AY,  
 -R<sup>10</sup>C(O)NHR<sup>10</sup>Het, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>9</sup>, -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>,  
 20 -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>NR<sup>7</sup>AY, -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>, cyano, nitro and  
 azido;

or two adjacent R<sup>1</sup> groups together with the carbon atoms to which they are  
 bonded form a cycloalkyl or a 5- or 6-membered heterocyclic group  
 containing 1 or 2 heteroatoms;

- 25 each R<sup>7</sup> and R<sup>8</sup> are the same or different and are independently selected from  
 the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl,  
 -C(O)R<sup>9</sup>, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>11</sup>, -C(S)NR<sup>9</sup>R<sup>11</sup>, -C(NH)NR<sup>9</sup>R<sup>11</sup>, -SO<sub>2</sub>R<sup>10</sup>,  
 -SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>9</sup>, -R<sup>10</sup>C(O)R<sup>9</sup>, -R<sup>10</sup>CO<sub>2</sub>R<sup>9</sup>,  
 -R<sup>10</sup>C(O)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(S)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>C(NH)NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>,  
 30 -R<sup>10</sup>SO<sub>2</sub>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>SO<sub>2</sub>NHCOR<sup>9</sup>, -R<sup>10</sup>NR<sup>9</sup>R<sup>11</sup>, -R<sup>10</sup>NHCOR<sup>9</sup>, -R<sup>10</sup>NHSO<sub>2</sub>R<sup>9</sup>  
 and -R<sup>10</sup>NHC(NH)NR<sup>9</sup>R<sup>11</sup>;

each  $R^9$  and  $R^{11}$  are the same or different and are independently selected from the group consisting of H, alkyl, cycloalkyl,  $-R^{10}$ cycloalkyl,  $-R^{10}OH$ ,  $-R^{10}(OR^{10})_w$  wherein  $w$  is 1–10, and  $-R^{10}NR^{10}R^{10}$ ;

each  $R^{10}$  is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

Ay is aryl;

Het is a 5- or 6-membered heterocyclic or heteroaryl group;

Y is N or CH;

$R^2$  is selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl,

10 Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-S(O)_nR^9$ ,  $-S(O)_nAy$ ,  $-S(O)_nHet$ ,  $-S(O)_nNR^7R^8$ ,  $-NR^7R^8$ ,  $-NHHet$ ,  $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

$n$  is 0, 1 or 2;

$R^3$  and  $R^4$  are the same or different and are each independently selected from the

15 group consisting of H, halo, alkyl, alkenyl, cycloalkyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-C(O)R^7$ ,  $C(O)AY$ ,  $-CO_2R^7$ ,  $-CO_2AY$ ,  $-SO_2NHR^9$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}OR^7$ ,  $-R^{10}OAY$ ,  $-R^{10}NR^7R^8$  and  $-R^{10}NR^7Ay$ ;

Ring A is a 5–10 membered heterocyclic or heteroaryl group;

$q$  is 0, 1, 2, 3, 4 or 5; and

each  $R^5$  is the same or different and is independently selected from the group

20 consisting of halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, Ay, Het,  $-OR^7$ ,  $-OAY$ ,  $-OR^{10}Ay$ ,  $-OHet$ ,  $-OR^{10}Het$ ,  $-C(O)R^9$ ,  $-C(O)AY$ ,  $-C(O)Het$ ,  $-CO_2R^9$ ,  $-C(O)NR^7R^8$ ,  $-C(O)NR^7Ay$ ,  $-C(O)NHR^{10}Het$ ,  $-C(S)NR^9R^{11}$ ,  $-C(NH)NR^7R^8$ ,  $-C(NH)NR^7Ay$ ,  $-S(O)_nR^9$ ,  $-S(O)_2NR^7R^8$ ,  $-S(O)_2NR^7Ay$ ,  $-NR^7R^8$ ,  $-NR^7Ay$ ,  $-NHHet$ ,  $-NHR^{10}Ay$ ,  $-NHR^{10}Het$ ,  $-R^{10}$ cycloalkyl,  $-R^{10}Het$ ,  $-R^{10}OR^9$ ,  $-R^{10}C(O)R^9$ ,  $-R^{10}CO_2R^9$ ,  
25  $-R^{10}C(O)NR^9R^{11}$ ,  $-R^{10}C(O)NR^7Ay$ ,  $-R^{10}C(O)NHR^{10}Het$ ,  $-R^{10}C(S)NR^9R^{11}$ ,  $-R^{10}C(NH)NR^9R^{11}$ ,  $-R^{10}SO_2R^9$ ,  $-R^{10}SO_2NR^9R^{11}$ ,  $-R^{10}SO_2NHCOR^9$ ,  $-R^{10}NR^7R^8$ ,  $-R^{10}NR^7Ay$ ,  $-R^{10}NHC(NH)NR^9R^{11}$ , cyano, nitro and azido;

wherein when Y is CH,  $R^3$  is not  $-NR^7Ay$ ; or a

pharmaceutically acceptable salt, solvate or physiologically functional derivative

30 thereof.

2. The compound according to claim 1 wherein p is 0, 1 or 2.
3. The compound according to claim 1 wherein p is 1.
- 5 4. The compound according to any of claims 1-3 wherein each R<sup>1</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, Ay, Het, -OR<sup>7</sup>, -OAY, -C(O)Het, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -C(O)NHR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHHet, -NHR<sup>10</sup>Ay, -NHR<sup>10</sup>Het, -R<sup>10</sup>OR<sup>9</sup>, cyano, nitro and azido.
- 10 5. The compound according to any of claims 1-3 wherein each R<sup>1</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, Het, -OR<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -S(O)<sub>n</sub>R<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay and -NHHet.
6. The compound according to any of claims 1-5 wherein R<sup>2</sup> is selected from the  
15 group consisting of Ay, Het, -OR<sup>7</sup>, -OHet, -OR<sup>10</sup>Het, -S(O)<sub>n</sub>R<sup>9</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NHHet, -NHR<sup>10</sup>Het and -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>.
7. The compound according to any of claims 1-5 wherein R<sup>2</sup> is selected from the  
20 group consisting of -NR<sup>7</sup>R<sup>8</sup> and Het.
8. The compound according to any of claims 1-7 wherein Y is N.
9. The compound according to any of claims 1-7 wherein Y is CH.
- 25 10. The compound according to any of claims 1-9 wherein R<sup>3</sup> and R<sup>4</sup> are the same or different and are each independently selected from the group consisting of H, halo, alkyl, Ay, -OR<sup>7</sup>, -CO<sub>2</sub>R<sup>7</sup>, -NR<sup>7</sup>R<sup>8</sup>, -R<sup>10</sup>OR<sup>7</sup> and -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup>.
11. The compound according to any of claims 1-9 wherein R<sup>3</sup> and R<sup>4</sup> are each H.
- 30 12. The compound according to any of claims 1-11 wherein Ring A is selected

from the group consisting of furan, pyridine, pyrimidine, thiazol, pyrazine, pyrrole, imidazole, oxazole, benzimidazole, quinoline, isoquinoline and quinoxoline.

13. The compound according to any of claims 1-11 wherein Ring A is selected from the group consisting of furan, thiazole, pyridine and pyrimidine.
14. The compound according to any of claims 1-13 wherein q is selected from the group consisting of 0, 1 and 2.
15. The compound according to any of claims 1-13 wherein q is 1.
16. The compound according to any of claims 1-15 wherein each R<sup>5</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, alkenyl, Ay, Het, -OR<sup>7</sup>, -OAy, -CO<sub>2</sub>R<sup>9</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>7</sup>Ay, -S(O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>Ay, -NHR<sup>10</sup>Ay, cyano, nitro and azido.
17. The compound according to any of claims 1-15, wherein each R<sup>5</sup> is the same or different and is independently selected from the group consisting of halo, alkyl, -OR<sup>7</sup>, -NR<sup>7</sup>R<sup>8</sup>, cyano, nitro and azido.
18. A compound selected from the group consisting of:  
*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-3-[2-(methylamino)-4-pyrimidinyl]-2-(4-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-pyridinyl)pyrazolo[1,5-*a*]pyridin-7-amine;  
*N*-Cyclopentyl-*N*-(4-{2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)amine;  
*N*-(4-{7-Chloro-2-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinyl)-*N*-cyclopentylamine;

- N*-Cyclopentyl-2,3-bis[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-(2-Methoxyethyl)-2,3-bis{2-[(2-methoxyethyl)amino]pyrimidin-4-yl}pyrazolo[1,5-*a*]pyridin-7-amine;
- 5 *N*-Butyl-2,3-bis[2-(butylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Cyclopropyl-2,3-bis[2-(cyclopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine;
- 7-Morpholin-4-yl-2,3-bis(2-morpholin-4-ylpyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine;
- N*-Isobutyl-2,3-bis[2-(isobutylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine;
- 10 *N*-Benzyl-2,3-bis[2-(benzylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Isopropyl-2,3-bis[2-(isopropylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine;
- 2-(2-Fluoro-4-pyridinyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine;
- 4-[2-(2-Fluoro-4-pyridinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-isopropyl-2-pyrimidinamine;
- 15 *N*-Isopropyl-4-{2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-3-yl}-2-pyrimidinamine;
- 3-[2-(Cyclopropylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Cyclopentyl-2-[2-(cyclopentylamino)-4-pyridinyl]-3-[2-(isopropylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine;
- 20 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-isopropyl-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-[2-(isopropylamino)-4-pyridinyl]pyrazolo[1,5-*a*]pyridin-7-amine;
- 25 *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;
- N*-Cyclopentyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;
- 30

*N*-Cyclopropyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(3-methyl-2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;

*N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;

5 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-*N*-cyclopropyl-2-(2-furyl)pyrazolo[1,5-*a*]pyridin-7-amine;

2-(5-Bromo-2-furyl)-*N*-cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine; and

10 *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyridinyl]-2-(2-methyl-1,3-thiazol-4-yl)pyrazolo[1,5-*a*]pyridin-7-amine;

or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

19. A pharmaceutical composition comprising a compound according to any of  
15 claims 1-18.

20. A pharmaceutical composition according to claim 19 further comprising a pharmaceutically acceptable carrier or diluent.

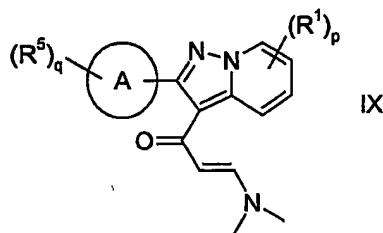
20 21. A pharmaceutical composition according to claim 19 further comprising an antiviral agent selected from the group consisting of aciclovir and valaciclovir.

22. A method for the prophylaxis or treatment of a herpes viral infection in an animal, said method comprising administering to the animal a therapeutically  
25 effective amount of a compound according to any of claims 1-18

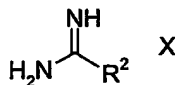
23. The method according to claim 22, wherein said herpes viral infection is selected from the group consisting of herpes simplex virus 1, herpes simplex virus 2, cytomegalovirus, Epstein Barr Virus, varicella zoster virus, human herpes virus 6,  
30 human herpes virus 7 and human herpes virus 8.

24. A method for the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal, comprising administering to the animal a therapeutically effective amount of a compound according to any of claims 1-18.

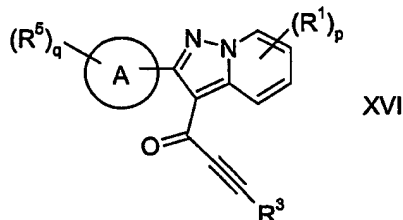
25. A process for preparing the compound according to any of claims 1-18 wherein Y is N and R<sup>3</sup> and R<sup>4</sup> are H; said process comprising reacting a compound of formula (IX):



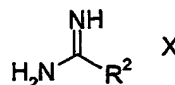
with a compound of formula (X):



26. A process for preparing the compound according to any of claims 1-18, wherein Y is N; R<sup>3</sup> is selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, Aryl, Het, -OR<sup>7</sup>, -OAr, -C(O)R<sup>7</sup>, C(O)Ar, -CO<sub>2</sub>R<sup>7</sup>, -CO<sub>2</sub>Ar, -SO<sub>2</sub>NHR<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup> (where R<sup>7</sup> and R<sup>8</sup> are not H), -NR<sup>7</sup>Ar (where R<sup>7</sup> is not H), -R<sup>10</sup>cycloalkyl, -R<sup>10</sup>OR<sup>7</sup>, -R<sup>10</sup>OAr, -R<sup>10</sup>NR<sup>7</sup>R<sup>8</sup> and -R<sup>10</sup>NR<sup>7</sup>Ar; and R<sup>4</sup> is H, said process comprising reacting a compound of formula (XVI):

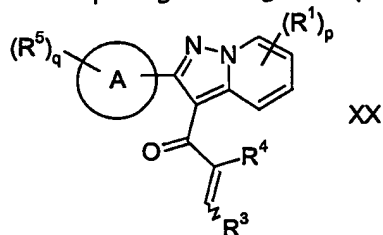


with a compound of formula (X):

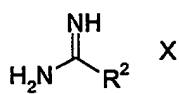


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27. A process for preparing the compound according to any of claims 1-18 wherein Y is N, said process comprising reacting a compound of formula (XX):

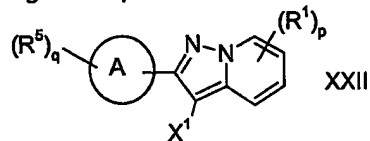


with a compound of formula (X):



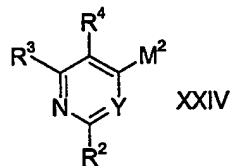
followed by oxidative aromatization.

28. A process for preparing the compound according to any of claims 1-18, said process comprising reacting a compound of formula (XXII):



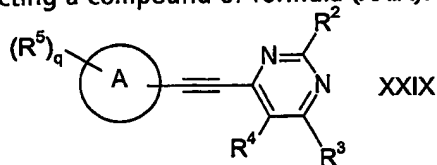
wherein X<sup>1</sup> is chloro, bromo or iodo;

with a compound of formula (XXIV):

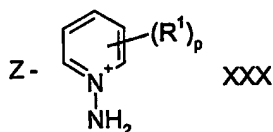


25 wherein M<sup>2</sup> is selected from the group consisting of -B(OH)<sub>2</sub>, -B(ORa)<sub>2</sub>, -B(Ra)<sub>2</sub>, -Sn(Ra)<sub>3</sub>, Zn-halide, ZnRa, and Mg-halide, where Ra is alkyl or cycloalkyl and halide is halo.

29. A process for preparing the compound according to any of claims 1-18, said process comprising reacting a compound of formula (XXIX):

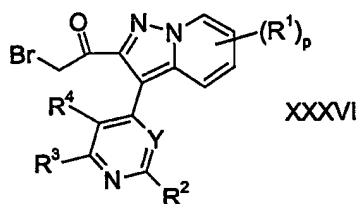


with a 1-aminopyridinium salt of formula (XXX):



wherein Z- is a counter ion.

30. A process for preparing the compound according to any of claims 1-18, said process comprising reacting a compound of formula (XXXVI):



20 with a suitable ring forming reagent.

31. The process according to any of claims 25-30 further comprising the step of converting a compound of formula (I) to a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

25

32. The process according to any of claims 25-31 further comprising the step of converting a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof to another compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

30

33. A compound according to any of claims 1-18 for use in therapy.

34. A compound according to any of claims 1-18, for use in the prophylaxis or treatment of a herpes viral infection in an animal.
35. A compound according to any of claims 1-18, for use in the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal.
36. The use of a compound according to any of claims 1-18, for the preparation of a medicament for the prophylaxis or treatment of a herpes viral infection in an animal.
37. The use of a compound according to any of claims 1-18 for the preparation of a medicament for the prophylaxis or treatment of a condition or disease associated with a herpes viral infection in an animal.
38. A pharmaceutical formulation comprising a compound according to any of claims 1-18 for use in the preparation of a medicament for the prophylaxis or treatment of a herpes viral infection in an animal.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/37052

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/44 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 59585 A (CAMDEN JAMES BERGER ; PROCTER & GAMBLE (US)) 25 November 1999 (1999-11-25) abstract	1-38
A	FR 2 757 059 A (RHONE POULENC RORER SA) 19 June 1998 (1998-06-19) abstract	1-38
A	WO 99 58523 A (CRICH JOYCE Z ; SEARLE & CO (US); COLLINS PAUL W (US); WEIER RICHAR) 18 November 1999 (1999-11-18) page 2; claims	1-38
A	WO 01 14375 A (BEATTIE JOHN FRANKLIN ; BREAUULT GLORIA ANNE (GB); JEWSBURY PHILLIP) 1 March 2001 (2001-03-01) claims; overlap	1-38
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

21 March 2003

Date of mailing of the international search report

28/03/2003

Name and mailing address of the ISA

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Authorized officer

Frelon, D

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 02/37052

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 379 979 A (FUJISAWA PHARMACEUTICAL CO) 1 August 1990 (1990-08-01) abstract; examples 54,55,59 -----	1-38

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 02/37052

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 22-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/37052

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# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 02/37052

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